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VOLUME 5 *Mayo Clinic Number* NUMBER 2

THE MEDICAL CLINICS OF NORTH AMERICA

SEPTEMBER, 1921

PHILADELPHIA AND LONDON

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PUBLISHED BI-MONTHLY (SIX NUMBERS A YEAR), BY W. B. SAUNDERS COMPANY, WEST WASHINGTON SQUARE, PHILADELPHIA

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6 December
1921
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Mayo Clinic Number

THE MEDICAL CLINICS
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RETINITIS OF ACUTE NEPHRITIS: REPORT OF 6 CASES

WILLIAM L. BENEDICT

THE visible changes that take place in the retina as a result of impairment of the function of the kidneys are characteristic of the change within the kidney, and indicate to some extent the quality and quantity of that change.

Diseases of the kidneys that are slowly progressive and do not seriously interfere with the elimination of ordinary urinary products may produce systemic changes that are compensated for in some manner without causing any noticeable break in the general health of the patient, but which, nevertheless, seriously impair his resistance.

There may be a series of slight attacks of inflammation of the kidney, each one producing a slight rise of temperature, malaise, headache, and a temporary rise of blood-pressure, which subsides without attracting serious attention. We may assume that a state of constant irritation and inflammation of the renal epithelium, of such low grade that the person would not be considered sick, might exist for years. Such a condition would be termed "chronic nephritis." Kidneys that have been inflamed repeatedly or that have been inflamed continuously for months or years may suddenly be overwhelmed by an attack that will seriously impair or arrest their function. Such an attack leads to changes in the retina which might be designated as *acute retinitis of nephritis*, but since the picture is rather peculiar and since acute retinitis from other causes

is common, it seems better to allude to this phenomenon as *retinitis of acute nephritis*, particularly since it occurs in the course of chronic nephritis only after an acute exacerbation, or a serious complication such as renal calculi. The relation of this form of retinitis to chronic nephritis and to vascular degeneration has been considered in a previous article.[1] The ophthalmoscopic picture of this type is not always accompanied by urinary changes or changes in the blood chemistry, and nephritis may be overlooked or denied on the evidence that can be deducted by laboratory tests. However, careful observation for a few days will nearly always result in finding analyses of the blood and urine positive for nitrogen retention and impaired function. The presence of the retinitis of acute nephritis, even in the absence of other signs or symptoms of nephritis, is sufficient to warrant the closest attention under the best conditions and continued observation with frequent tests. In order to emphasize the relationship of the retinitis of acute nephritis to nephritis in general I shall report the following cases somewhat in detail:

Case I (256,254), a woman aged forty-seven years, was examined January 15, 1919. She gave a history of frequent headaches since childhood, and at a previous examination in the Clinic was reported to have migraine. Ten years before her systolic blood-pressure had been 180. One month previous to her examination it had suddenly become necessary for her to empty her bladder every ten or fifteen minutes during the day and hourly during the night. She suffered from severe frequent pains radiating to the kidneys, more to the right, although slightly to the left. The pains continued for several days with sufficient severity to require morphin. After eight days of frequent voiding she had no further symptoms. A cystoscopic examination was made by a local physician, who diagnosed tuberculosis of the bladder and probably of the right kidney. She had had no symptoms of bladder or kidney disease since then, but complained of nervousness and inability to sleep.

The patient felt well except for an occasional headache. The systolic blood-pressure was 210; the diastolic, 120; the

pulse, 91. There was slight edema of the lower extremities. A urinalysis of 2000 c.c. (twenty-four-hour specimen) revealed a specific gravity of 1.008, a small amount of albumin, and an occasional hyaline cast. A combined phenolsulphonephthalein test of renal function gave a return of 50 per cent. in two hours and fifteen minutes. There were 15 mg. of blood urea per 100 c.c. of blood. A cystoscopic examination of the urinary tract was negative; the bladder and both kidneys were found to be quite normal. The heart was slightly hypertrophied. The Wassermann reaction on the blood was negative. On examination of the fundus oculi marked vascular changes of hypertension were found. The diagnosis was hypertension, with early interstitial nephritis.

February 5, 1921 the patient came for re-examination. Two months before her tonsils had been removed. Since then she had suffered from headache, backache, nausea, and vomiting. She had been in bed for ten days because of a cold in the chest. She had not felt well since, and complained of pain in the right side. The systolic blood-pressure was 220; the diastolic, 124; the pulse, 96; the blood urea was 30 mg. per 100 c.c. A combined phenolsulphonephthalein test of renal function gave a return of 55 per cent. in two hours and fifteen minutes. Urinalysis of 1650 c.c. (twenty-four-hour specimen) revealed a specific gravity of 1.010, a slight amount of albumin and casts. The vision of each eye was 6/6 with glasses. Retinitis of acute nephritis was diagnosed after ophthalmoscopic examination. The retinal arteries were not much thickened and there was little arteriovenous compression.

February 18, 1921 there was marked exaggeration of the arterial reflex in both eyes, with sharp compression of the veins by the arteries. In the right eye a "snowbank" exudate extending upward and nasally from the disk was undergoing absorption. In the left eye were several petechial hemorrhages, also extending upward and nasally from the disk. From February 7, 1921 to February 19, 1921 only a slight amount or no albumin was found in the urine. Casts were found only occasionally; uric acid was 3.1 to 2.5 mg. per 100 c.c.; creatinin 1.32 to 1.35

mg. per 100 c.c.; and blood urea 30 to 36.2 mg. per 100 c.c. The phenolsulphonephthalein test of renal function showed improvement of the kidneys by the increase in phenolsulphonephthalein return of from 55 to 70 per cent. (February 18, 1921) in two hours and fifteen minutes. The systolic blood-pressure came down from 220 to 164, and the diastolic from 124 to 108. At the time of the patient's dismissal she had good renal function, normal blood urea, slight or no albuminuria, no casts or cellular elements in the urine, and only moderately increased blood-pressure.

The retinitis observed in this case was characteristic of the lesion produced by a renal break in a patient who has had high blood-pressure of varying degree for several years which has produced a moderate sclerosis of the retinal arteries.

Case II (344,317). A man aged forty years came for examination December 21, 1920. In May, 1920 his sight had begun to fail; at first there had been spots before the eyes. For the last year he had been voiding two or three times during the night, and recently from four to seven times. For the past two months his visual acuity had been reduced to scant ability to distinguish fingers, and for this reason he had been unable to carry on his work as section-hand on the railroad. December 25, 1920 urinalysis showed specific gravity 1.006; albumin a trace; and a few casts. There were 23 to 25 mg. of blood urea per 100 c.c. A phenolsulphonephthalein test of renal function showed a return of 55 per cent. on one occasion and of 50 per cent. on repetition.

On examination of the fundus oculi (December 27, 1920) the nerve heads of both eyes were found to be markedly swollen (about 6 or 7 diopters), with exudate surrounding the disks, parts of which stopped abruptly, while other parts faded gradually into the surrounding retina at some distance from the disk. On the surface of this exudate and on the disk (the disk limits could not well be ascertained) were numerous flame-shaped hemorrhages. In the right eye beyond the limits of the exudate were also some round, deeper hemorrhages, some punctate exudates, and a few which suggested "cotton-wool,"

though not typical. In both eyes were numerous peripheral areas of old pigmented chorioretinitis. This was believed to indicate two processes: choked disk on an old neurochorioretinitis, with probably some recent retinitis. There was nothing in the neurologic data aside from the ophthalmic findings to suggest intracranial pressure (Woltman). A roentgenogram of the skull for signs of intracranial disease was negative. The Wassermann reaction on the spinal fluid was negative. A Nonne test was positive, and two small lymphocytes to the field were found. December 31, 1920 the specific gravity of the urine was 1.007; albumin was slight; a few casts were found. There were 34 mg. of blood urea per 100 c.c. A phenolsulphonephthalein test gave a return of 40 per cent. in two hours and fifteen minutes. The systolic blood-pressure was 220, the diastolic 160. Ophthalmoscopic examination showed swelling of the disks, now measurable as 6 diopters in the right eye and 4 diopters in the left eye. An area of grayish retinal edema extending nasalward to the disk in the left eye suggested a commencing retinal detachment. January 8, 1921 the swelling of the disks was measured as 4 to 5 diopters in both eyes. The margins of the nerve heads were still indistinguishable and the surrounding edema was more extensive. In the right eye in the far nasal area and in the far temporal lower periphery were areas of intense retinal edema which suggested detachment of the retina. The area in the left eye, which previously had been noted nasalward to the disk, had become a definite detachment which connected in the lower periphery with a diffuse lobulated detachment. In the temporal periphery was a localized, circumscribed retinal detachment two or three disk diameters in size. January 11, 1921 the blood urea had increased to 41.8 mg. per 100 c.c., and a phenolsulphonephthalein test of renal function gave a return of only 25 per cent. January 12, 1921 the edema in the lower nasal retina in the right eye had developed into a definite retinal detachment. The area of detachment in the temporal periphery of the left eye had also become more extensive. January 24, 1921 the retinal detachment involved the entire lower periphery of both fundi, the

vessels on the surface being seen with a +14 to +16 lens. The retina in the region of the disk was still elevated and full of exudate, and there were numerous fresh hemorrhages in the retina of the right eye. The upper part of the right retina seemed to be edematous. The specific gravity of the urine was about 1.006; the urine was heavily loaded with albumin and casts, both being graded as 3 on a scale of 1, 2, 3, 4. There were 38 mg. of blood urea per 100 c.c. The systolic blood-pressure was 240, the diastolic 140. The blood uric acid and creatinin did not increase and there was not much increase in casts. This was considered a marked case of hypertension on a nephritic basis.

The patient when first examined had a severe neuroretinitis of a type that indicated marked damage to the kidneys. A functional test of the kidneys revealed very little evidence of the severity of the process, and since the patient complained more of his loss of vision than anything else he was not considered sufficiently ill to need immediate hospitalization. He was placed in the hospital, however, after the ophthalmoscopic examination revealed the severity of the affection. Only after several days of observation the kidney affection became manifest. Coincident with the decrease in renal function the violence of the retinitis increased, and when the patient passed from observation there had been no improvement in the condition of the eyes or of the kidneys.

Case III (346,351). A man aged fifty-four years was first examined January 13, 1921. His chief complaint was vomiting and slight intestinal cramps.

Urinalysis showed a slight amount of albumin, some hyaline casts, and occasional red and white blood-cells. The phenol-sulphonephthalein excretion was 32 per cent. in two hours. A roentgenogram of the kidneys revealed a small stone in the right kidney region. Ophthalmoscopic examination showed some retinal arteriosclerosis, but definite exudate or hemorrhages were not seen.

January 21, 1921 the fundus was examined again. One small area in the right eye above the disk faintly suggested

exudate, but definite exudate, edema, or hemorrhages were not found. The retinal picture was that of hypertension with secondary fibrosis. At this time there were 42 mg. of blood urea per 100 c.c., quite a normal amount. The systolic blood-pressure was 185; the diastolic, 95. January 18, 1921 the phenolsulphonephthalein test gave a return of 20 per cent.; January 19th, 30 per cent., January 24th, 35 per cent. At the last two tests the phenolsulphonephthalein was injected into a vein. The patient was dismissed from the hospital January 29th.

The patient remained well until February 18th. February 21st he became nauseated, and had fever and chills. He returned to the Clinic and was again admitted to the hospital. At this time he was somewhat drowsy and slightly nauseated. There were 84 mg. of blood urea and 1.9 mg. of creatinin per 100 c.c. The systolic blood-pressure was 128; the diastolic, 82. The phenolsulphonephthalein excretion was 32 per cent. in two hours and fifteen minutes. He was slightly feverish. The functional studies completed February 26th showed the phenolsulphonephthalein excretion to be 50 per cent.; creatinin and carbon dioxid were in normal amounts in the blood. Eye-grounds in both eyes, besides the vascular condition previously mentioned, showed some areas of exudate. March 1st there were areas of "cotton-wool" exudate in the superior temporal regions of both eyes. The disk margins were still distinct. There was no definite neuritis and no retinal hemorrhages. March 6th an area of exudate appeared in the nasal quadrant of the left eye.

The uremic symptoms which came on about February 18th were attributed by Dr. Braasch to blockage of the right kidney by stone. The clinical findings, together with the previous history of high blood-pressure and high blood urea, made us believe that the patient had had a definite nephritis. On his dismissal, April 18th, the systolic blood-pressure was 140; the diastolic, 100. A phenolsulphonephthalein test of the renal function showed excretion to be 50 per cent. in two hours. The urea, creatinin, and uric acid content in the blood were normal. There was no albumin in the urine, no casts or red

cells, but there were still some pus-cells. The systolic blood-pressure occasionally reached 170. The fundus examination April 16th showed wide arterial reflex, relatively engorged veins, arteriovenous compression, and arteriosclerosis consecutive on hypertension. There were no edema, hemorrhages, or exudates seen. We were fortunate in our observation of this case to be able to have for reference full clinical data and laboratory reports on urinalysis and chemical examinations of the blood both before and after a decided break in the function of the kidney.

The seizure in February, 1921, during which the patient suffered from dizziness, weakness, nausea, and vomiting, was a repetition of previous attacks. The home physician who attended him during the last attack stated that there were symptoms of uremia, and this diagnosis was supported by the opinion of the physicians who examined him at the Clinic. For three days there had been signs of marked impairment of renal function. For the next few days recovery was rapid, after which convalescence was slower, but, nevertheless, was uninterrupted. The changes in the retina which have been described as characteristic of such renal impairment became more marked even during the period of convalescence, and later cleared away entirely, leaving no definite visible evidence of what had taken place. The retinal picture resumed its former appearance even as the urine and blood became normal, and only the hypertension continued as a physical evidence of the succession of breaks of renal function. The sclerosis of the retinal arteries characteristic of hypertension remained as additional and visible evidence. All signs of the attack of acute nephritis had disappeared within two months after it had occurred.

Case IV (353,904). A woman aged forty-three years came for examination March 30, 1921. Her chief complaint was general weakness. Her general condition had been good until four years before, when she gave birth to a baby at eight months. Since then she had lost 75 pounds in weight. She had not taken her temperature, but did not think she had had fever. During the last three years she had had occasional frequency

without hematuria or high urea. For the past two months she had been having night-sweats and rheumatism, and had been unable to see well with her left eye, the field of vision of which was peripherally diminished.

General examination showed the heart to be markedly enlarged to the left and to the right. The radial arteries were sclerosed. The systolic blood-pressure was 244, diastolic 140, the pulse 108. The specific gravity of the urine was 1.014; it contained a slight amount of albumin. A roentgenogram of the chest showed tuberculosis of both upper lobes. A serum Wassermann reaction was negative. The sputum was examined on four different occasions; tuberculosis bacilli were found on the third examination only. Ophthalmoscopic examination showed that the optic disk in the right eye was hyperemic and edematous (1 diopter). The veins were quite tortuous, the arteries very much reduced and irregular in caliber. A marked arteriovenous compression was noted. One area of "cotton-wool" exudate was seen, but there were no hemorrhages. In the left eye the optic disk was yellowish white and the margins were blurred. The veins were tortuous and very irregular in caliber. Arteriovenous compression was noted here also, and one partially absorbed hemorrhage was seen.

This picture suggested a severe neuroretinitis of nephritis in both eyes and arteriosclerosis secondary to hypertension, with secondary optic atrophy in the left eye. The possibility of embolism of the central artery in the left eye was considered in view of a history of sudden blindness. The right pupil reacted normally, the left pupil reacted but little, except to consensual light. The left eye had only light perception. Records of laboratory tests show, briefly, the course of the disease while under observation:

April 1st blood urea 38 mg. per 100 c.c.; April 2d examination of 500 c.c. of urine (twelve-hour specimen) showed specific gravity 1.016, albumin 2, and no casts. (The amount of albumin in the urine is estimated by the appearance of the precipitate brought down by use of heat and nitric acid. It is recorded on a scale of 1, 2, 3, 4.) April 4th examination of 1300 c.c. of

urine (twelve-hour specimen) showed specific gravity 1.013 and albumin 2. Microscopic examination was negative. Phenolsulphonephthalein excretion was 47 per cent. Repetition (no date given) showed 60 per cent. excretion. April 11th blood urea was 54 mg. per 100 c.c., and April 15th examination of 1700 c.c. of urine (twelve-hour specimen) showed specific gravity 1.021, albumin 1, and casts 1. Blood urea was 38 mg. per 100 c.c. April 18th examination of 550 c.c. of urine (twelve-hour specimen) showed specific gravity 1.020, albumin 1, and casts 1. Blood urea was 54 mg. per 100 c.c. Systolic blood-pressure was 288; the diastolic, 151. April 19th phenolsulphonephthalein excretion was 20 per cent. in two hours and fifteen minutes. April 25th blood urea was 46 mg. per 100 c.c. The systolic blood-pressure was 233; the diastolic, 92.

During the patient's stay in the hospital (from April 15th to April 25th) the urine remained free from albumin and casts, and only from 2 to 5 pus-cells to the field were found by microscopic examination of the sediment. There was no increase in uric acid and creatinin in the blood. Only a slight decrease in blood-pressure was noted. There was marked decrease in renal function, as shown in the phenolsulphonephthalein test, and an increase in the blood urea. April 16th the ophthalmoscopic examination of the right eye showed that the edema of the nerve head and retina had increased. The disk was now swollen about 4 diopters. The retinal arteries were small, tortuous, and hard to follow. Arteriovenous compression was marked. There were two or three areas of "cotton-wool" exudate in the upper temporal quadrants of the retina of both eyes. A few small hemorrhages were located near the exudates. The disk of the left eye was still yellowish white and edematous, but the swelling was not measureable. The arteries could be followed more easily than in the right eye because of less retinal edema; they could be seen to be markedly contracted, irregular in caliber, and tortuous. There was marked arteriovenous compression, with several rather large hemorrhages, one or two of which were recent, and one or two were absorbing. April 21st there was no material change in the appearance of the fundus.

Case V (370,157). A woman aged forty-five years was examined August 26, 1921. She had considered herself well until February 1, 1921, when she had had a "stroke." She suddenly became unconscious for a moment, and was not able to talk. For several days afterward she noticed weakness in moving the right arm and leg. Since then she had led an invalid's life, with weakness as her chief complaint. She had had a steady ringing in her ears. Her sight had failed rapidly, she had dyspnea on exertion, and had some headache around the top of the head. For several years before the onset of the stroke she had noticed a slight tendency to edema of the feet. In February, 1921 her blood-pressure was said to be 240.

The patient's normal weight was 214 pounds, her present weight 143 pounds. The heart was enlarged, its action regular and rapid; pulmonary edema was not present. There was no ascites, although the liver was enlarged and tender. Her entire right side was weak, evidence of a former hemiplegia. The systolic blood-pressure was 240, the diastolic 140, and the pulse 120. The fluid output amounted to about 325 c.c. in twelve hours. There was only a faint trace of albumin, an occasional hyaline cast, and a few pus-cells. In the blood there were 1.9 mg. of creatinin and 34 mg. of urea per 100 c.c. The diastolic and systolic blood-pressures were not lowered during the six days she was under observation. A phenolsulphonephthalein test of the renal function was not made. The ophthalmoscopic examination showed rather marked edema of the optic disks and retina. The disk of the right eye was swollen about 3 diopters, the disk of the left eye about 1 diopter. There was a marked engorgement of the veins with tortuosity of the arteries, marked edema of the whole retina, areas of white exudate of "cotton-wool" type, and many large and small hemorrhages. In the macular region of the right eye there was a massive exudate. In the periphery of both eyes there were several small areas of old choroiditis, with pigment migration, which suggested that there had been previous attacks of inflammation. Very little evidence of nephritis was obtained by urinalysis, although the history of high blood-pressure indi-

cated malignant hypertension. The arteriosclerosis was not marked in the retina, but there was a violent active retinitis characteristic of intense renal damage.

Six days after the patient's admission to the hospital she had a large cerebral hemorrhage which was responsible for her death. At necropsy the kidneys were found to be small, red and granular, with adherent capsule and marked arteriosclerosis. While the patient's blood urea had not been high at the time of her examination, and her renal function not seriously impaired, the extreme hypertension with vascular degeneration was a complication too heavy to be borne.

The changes that take place in the eye-grounds during an attack of nephritis are dependent on several factors not all of which are well understood. The frequent finding of albuminuric retinitis in a person whose urine examination and renal functional tests are not indicative of serious renal impairment have tended to throw doubt on the significance of the retinal picture, and to warrant the presumption that arteriosclerosis or some toxic substance in the blood also produces retinitis that to all appearances is identical with the changes most frequently found in Bright's disease. Certainly the presence of albumin in the urine is not necessary to establish a retinitis of this type, and when renal function is good, there seems to be little ground on which to claim a direct causal relationship.

Sclerosis or fibrosis of the retinal arteries has been held to play an important part in the production of the retinal changes. As a primary disease of the vessels it no doubt does have an important bearing on the nutrition of the retina. Sclerosis of these vessels consequent to hypertension or some vascular disease produces changes in the retina that are well known. Albuminuric retinitis has been ascribed to both of these causes, either acting alone or in conjunction with some other factor, most often cardiac hypertrophy and nephritis.

The frequency with which albuminuric retinitis appears in children and young adults has detracted from the hypothesis that slight vascular degeneration, in addition to other factors, is required to produce albuminuric retinitis. Thus while the

retinal pictures of changes produced by nephritis and by vascular degeneration have much in common, and may often be identical, the active agent in the production of the change cannot be the same. Retinitis of arteriosclerosis is not the same as the retinitis of nephritis, although both conditions may be present in the same eye at the same time. Retinitis of nephritis follows directly a break in renal function, although the connection is too often clouded by lack of clinical and laboratory data. Rochon-Duvigneaud states that "it is unnecessary to consider general arterial degeneration as the intermediary between the disease of the kidneys and the ocular lesions. Nephritis and retinitis are not two associated lesions, dependent on a common cause, acting individually on the kidney and retina. The retinitis is subordinate to the nephritis and is to be considered as a local phenomenon in patients whose only constant lesions are renal mischief and cardiac hypertrophy. The diseased kidney is the cause of the retinal lesions not because of any particular type of organ, for example, the contracted granular kidney, but because of deficient elimination and the retention of urea or some substance intimately related to urea."

Retinitis of acute nephritis occurs when there has been severe impairment of renal function. It is not necessary to assume that the kidneys were previously healthy. It does mean, however, that an accumulation of products ordinarily eliminated by the kidney is loading the blood to the detriment of body tissues, and if it reaches beyond bodily tolerance, either in amount or time, the result will be registered in tissue damage of a proportionate degree. Regardless of what else may befall a retina, the presence of these substances in the blood produces changes characteristic, if not pathognomonic of nephritis, and the cases reported herein indicate that with the lessening of elimination by the kidneys there is an increase in the violence of the retinitis. There is a stumbling-block in this line of reasoning in the time required for a renal break to produce the changes in the retina. An attack of acute nephritis lasting a day or a few days may occur in a person whose kidneys have suffered from previous attacks of greater or less severity. A person may have chronic nephritis of any type with good elimination

until from exposure, diet indiscretion, infection, or stone he may suffer from temporary blockage of the kidney. Within a few days symptoms of uremia may follow, which may go on to death, or the patient may recover. Uremia is a condition of comparatively short duration. Patients who recover have usually a profound retinitis of the type described as due to acute nephritis, but the retinitis may be delayed for days or even weeks after the onset of the attack. I shall not discuss here the pathology of retinitis, but will say that the return of the retina to normal appearance, which will occur if no further insult is added to the original injury, takes a much longer time than is required for the demonstration by the phenolsulphonephthalein test that the kidneys have good function or that the urine has become normal. Hence, for several days or weeks after all other signs of arrested elimination of the kidney have disappeared the retina will distinctly indicate what has taken place, about how long the interference lasted, and approximately when it occurred. Mild retinitis of acute nephritis will disappear within six weeks of its appearance and within two months of the attack of nephritis. Attacks of acute nephritis may occur at any age or state of health. They may come as incidents in chronic nephritis or nephritis of arteriosclerosis. Retinitis is not dependent on the vascular condition of either the kidney or the retina, but on the functional incapacity of the kidneys. It may come with few symptoms or other signs of nephritis, and it may be absent in terminal uremia. It seems to be an aftermath to retinal damage by some extraneous agent, as the black-and-blue discoloration in the skin following a blow on the arm is an aftermath; as the pain and loss of function of the arm may disappear often before the discoloration is noticed, just so the physical signs of nephritis, and the evidences of impaired renal elimination may be absent, the patient may have recovered from the nephritis, yet the signs still be present in the ocular fundus.

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OBSERVATIONS ON THE SPHENOPALATINE GANGLION SYNDROME OF THE SYMPATHETIC TYPE: REPORT OF 3 CASES

ROY A. BARLOW

REPEATED paroxysms of sneezing are so commonly attributed to so-called hay-fever that it seems fitting to call attention to a phenomenon simulating this condition which is due to an irritation of the sphenopalatine or nasal ganglion. I do not wish to convey the impression that all hay-fever is a nasal ganglion manifestation, but to point out the fact that the condition of some of these patients has been incorrectly diagnosed and they have been advised to seek some northern climate when the paroxysms could have been controlled and the patients made comfortable or cured at home. Observations of this syndrome have been reported by Fraser and Sluder.

THE ANATOMY OF THE SPHENOPALATINE GANGLION

The sphenopalatine ganglion is the most superficial sympathetic ganglion in the body; it lies just beneath the mucous membrane in the upper part of the sphenomaxillary fossa. It is a small triangular body consisting of fine interlacings of fibers with neurones from the sympathetic system. In a recent article on sphenopalatine headaches I called attention to the fact that the preganglionic and postganglionic fibers compose the efferent nerve mechanism. The postganglionic fibers influence the relaxation of the muscle-fibers of the blood-vessels. The preganglionic fibers originate in the nerve-cells of the gray matter beneath the floor of the fourth ventricle and emerge forward from the medulla between the seventh and eighth cranial nerves as the pars intermedia, and accompany the facial nerve to the geniculate ganglion, and then pass forward as the great superficial petrosal nerve to the sphenopalatine

ganglion. The peripheral nerve filaments proceed to the glands and arterioles of the mucous membrane lining of the nose and nasopharynx. As the great petrosal nerve passes the internal carotid arteries sympathetic fibers are picked up. Thus the blood-supply of the nose is under the control of the vasoconstrictor and vasodilator centers of the brain.

It is reasonable to assume that the tonicity of the vasoconstrictors and vasodilators may be altered by metabolic disturbances. The superficial position of the ganglion renders it vulnerable to outside stimuli, such as infection in the nasal chamber, dust, cold-air currents, etc.

CLINICAL MANIFESTATIONS

Sphenopalatine disturbances are of two types—the neuralgic and the sympathetic.

The patients with neuralgic disturbances complain of severe lower half headaches.

The patients with sympathetic disturbances have sneezing, lacrimation, and hay-fever-like attacks. The sneezing is persistant, often in paroxysms. The most outstanding feature is that the spells are not dependent on season or climate. The patients are just as uncomfortable in winter as in summer, in the mountains as on the plains. The symptoms are often so severe as to incapacitate persons in their daily work. The histories of three typical cases are as follows:

Case I (199,479). Mr. W. H. S., a business man, aged sixty-two years, had had attacks of sneezing with increasing frequency and severity for three years. His occupation had been severely interfered with. He had sought relief in the South, the West, and the North; he had had vaccines, tonics, and had altered his diet without relief. The sneezing and lacrimation and the stuffy sensation in the nose prevented him from attending business meetings; in fact, he had been forced to retire.

The patient was referred to me April 9, 1920 from the general diagnostic service, with a questionable diagnosis of hay-fever. He told me that his attacks were as severe in winter as in summer. Examination revealed congested and somewhat cyanotic nasal

mucosa, and the turbinates bathed in a watery secretion. No evidence of sinusitis was found; Roentgen-ray examination of the sinus was negative. The general health was good.

April, 1920 the patient's nasal ganglion was cocainized with 10 per cent. cocain and treated with 50 per cent. silver nitrate, applied to the mucosa over the ganglion. The next ten hours he was miserable; the sneezing was very severe, the nose was blocked, rhinorrhea was profuse, and there were some pain and headache. These symptoms subsided, and at the end of twenty-four hours he was much more comfortable. The treatment was repeated on alternate days until three had been given. Each treatment was followed by reactions of decreasing severity. After two weeks he was quite comfortable and the attacks of sneezing had ceased. He was dismissed from the Clinic at this time. One year later the patient called at the Clinic and reported that he had resumed his business activities, and had had no further trouble.

Case II (351,732). Mrs. J. S. Z., aged forty years, came to the clinic March 7, 1921 because of gall-bladder trouble, for which surgery was advised. She stated that she had attacks of sneezing without regard to season or locality and that she had been told that she had hay-fever.

Examination revealed septic tonsils and boggy and turgescent nasal mucous membrane, but no evidence of sinusitis. Considerable watery secretion bathed all the membranes. Examination of the ears was negative. Roentgen-ray examination of the sinuses was negative. Her general condition was good, except for the symptoms of gall-bladder trouble. She stated that at times the sneezing attacks were so violent that buttons burst from her clothing. Because of her history and the violence of the attacks while she was at the Clinic it was not deemed wise to operate on the gall-bladder because of the danger of a hernia should she have attacks during her convalescence.

March 4, 1921 the patient's nose was cocainized and the sphenopalatine fossa was treated with 50 per cent. silver nitrate. She spent the next twenty-four hours in sneezing; this gradually subsided. The treatment was repeated on the third day, with

less marked reaction. After a period of seven weeks, during which time she went home, she presented herself for reconsideration of the gall-bladder operation. She had not sneezed since her recovery from the last treatment, and she felt like a different person. A cholecystectomy was performed and the patient recovered uneventfully. Tonsillectomy was then performed. The nose was quite normal; there was very little secretion, and the cyanotic, boggy appearance of the mucous membranes noted at the first examination had disappeared.

Case III (359,123). Dr. D. D. T., aged thirty-six years, was examined in the Clinic March 23, 1921. The patient was in good general condition. His tonsils had been removed. His ears were normal. The condition of his nose was similar to that of the patient in Case II, and he gave a history of sneezing attacks, winters and summers, of four years' standing. Examination of the sinuses was negative.

March 24, 1921 the patient was treated with 50 per cent. silver nitrate; the reaction was like that in Cases I and II. The patient left the Clinic five days later. In subsequent letters he states that for five months he has had no further severe attacks. Occasionally he has sneezed three or four times in succession. There may be a few fibers which were not affected by the treatment and another application may be necessary.

TECHNIC OF TREATMENT

The technic is simple. The nasal ganglion is first cocainized by passing an applicator with cotton dipped in 10 per cent. cocain into the nose to the posterior end of the middle turbinate, since the ganglion lies just lateral to the posterior tip. This cocain applicator is allowed to remain in position about two minutes, after which it is withdrawn. A second applicator is dipped in sterile water, inserted to the same spot, and allowed to remain in position about one minute. The patient is told to note any symptoms which may appear, and to report the following day. This procedure rules out malingering and functional disorders. If the patient shows no effect by the second day, he is again cocainized. The second applicator is dipped in

50 per cent. silver nitrate solution instead of sterile water, all excess solution being squeezed out. This is allowed to remain in position about thirty seconds. This treatment is applied to both sides. The patient is instructed that he may have a severe sneezing spell over a prolonged period and that he is to report daily. About the third day the treatment is repeated. As a general rule two treatments are sufficient.

COMMENT

The ganglion may be injected with alcohol as in the neuralgic types of nasal ganglion disturbances, but I have found the silver nitrate treatment equally efficacious, since silver has a certain selectivity for nerve-tissue, as is illustrated in laboratory technic in which silver is employed to demonstrate nerve-fibers. The application of silver is less technical than the injection of alcohol; the technic is simpler, and complications are less liable to develop.

In conclusion I would state that if a patient complains of sneezing attacks simulating hay-fever and the paroxysms are not related to season or climate, dust, or altitude, the sphenopalatine ganglion should be considered a factor. It may be that the nasal ganglion in these patients is more superficially placed than in the average person, and this also may be the reason why local application gives relief. The superficial position of the ganglion renders it particularly sensitive to external irritation. There may also be other factors. These sphenopalatine cases are not found often, but they are found often enough to warrant being alert to their existence.

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CLINICAL AND SURGICAL EXPERIENCE IN DISEASES OF THE CHEST WITH SPECIAL REFERENCE TO PNEUMOTHORAX[1]

WILLIS S. LEMON AND ARLIE R. BARNES

THE problems of pneumothorax were subjects of discussion by physicians more than one hundred years ago. In their biographies and writings is an ever-moving and interesting story full of facts and fancies, of points settled and of others sharply debated. It is quite unnecessary to repeat the names of the writers who have aided so much our understanding of the condition, since this data has already been reviewed by several men in this country, especially by Emerson, who has brought it up to modern times and has added the reports of his own researches. This work, however, appeared in 1903, and in the hiatus of eighteen years the world has advanced, new events have elaborated new problems, and called for new solutions of old questions.

Four distinct factors have influenced our conception of pneumothorax and our methods of treatment: (1) the astonishing advancement of roentgenology as an aid in diagnosis, (2) the improved methods of the administration of local anesthesia, (3) a great war, and (4) a great pestilence. We cannot say too much of the importance of the Roentgen ray as an aid in accurate diagnosis. It is invaluable in many types of pneumothorax, especially in the small encapsulated hydropneumothoraces described by Sampson, Heise, and Brown, in small collections in the presence of much fluid, in larger collections when local adhesions prevent entire collapse of the lungs, and in the group in which the percussion note may be normal and

[1] Presented before the Fourth Annual Meeting of the American Association for Thoracic Surgery, Boston, June, 1921.

the position of the mediastinum unaffected because of pre-existing chronic inflammatory disease.

Because of the accuracy of roentgenology, however, there is a tendency to overlook the value of an accurate history and of a painstaking physical examination. One cannot understand pneumothorax by the mere examination of a negative any more than one can understand tuberculosis by finding the bacilli in the sputum, a technical accomplishment that can be shared by an office assistant. Yet, properly evaluated, each method is essential and each has materially increased our knowledge. The remarkable improvement in local anesthesia within recent years has made it possible to do away with much of the apparatus of the past. Local anesthesia relieves the surgeon of much of the dread of open pneumothorax. He can operate through a wound large enough to admit the hand; he can keep the lung expanded by the simple expedient of co-operating with a conscious patient; he can prevent danger by quickly converting an open into a closed pneumothorax at the first sign of danger; he can operate in stages without subjecting the patient to the danger of repeated general anesthesia; and finally, he may have a feeling of comparative assurance against the complications incident to the use of an irritating general anesthetic.

Local anesthesia is the method preferred when open pneumothorax is to be induced. In almost all cases it is sufficient if preceded by a narcotic. If general anesthesia is necessary, gas-oxygen is indicated, and ether, in our opinion, is to be preferred to chloroform, although some surgeons still use this dangerous drug.

The great war and almost simultaneously a great epidemic gave material in abundance for the extensive practice of thoracic surgery, and resulted in a very markedly improved diagnostic accuracy and an addition to our knowledge, because necessity awoke interest and interest prompted experiment. It is difficult to know to whom credit is due for our improvement in the treatment of influenzal empyema; so many workers arrived at the same conclusion simultaneously, although the Empyema Commission authorized various procedures under which the

work was conducted. Accustomed as we were to only one type of empyema, and almost wholly unacquainted with the streptococcal variety, many lives were lost because of early open operation. Graham and Bell studied this problem from a threefold viewpoint: (1) the effects of an open pneumothorax in normal and in diseased chests; (2) the experimental production of streptococcal pneumonia and empyema in dogs for comparison with the same disease in man; and (3) the effect of early operation in dogs with experimental streptococcal empyema. From these experiments they were able to advance an entirely new conception of open pneumothorax and to measure with mathematic accuracy the size of opening in the chest wall compatible with life. The limits, however, are large and are determined by so many factors that in practical surgery they have not been accepted as a working basis for operative procedures. From our own study we have been unable to accept the hypothesis in its entirety. When our patients are referred to Dr. Hedblom or to Dr. Lockwood for operation, the condition of each patient determines the location and the size of the thoracic opening. The size of the opening, in our experience, is not a differential surgical risk, and the operation is performed without pressure, but preferably with local anesthesia. The need for using pressure has been seen but rarely, and the opening of choice is the one best designed to permit the proper exposure and the necessary manipulation.

In order to estimate with exactness the relative importance of open pneumothorax in thoracic surgery and the frequency with which special methods of anesthesia are required for its control a survey of 498 operations has been made (Table I, page 298).

TABLE I

RESULTS OF 498 OPERATIONS ON 300 PATIENTS WITH THORACIC DISEASES

Diagnosis

Postpneumonic empyema, encapsulated or chronic	136
Pleurisy with effusion	107
Complications: Tuberculosis 19; primary or metastatic malignancy 22.	
Non-tuberculous sinuses	13
Hydropneumothorax, hemopneumothorax, or pyopneumothorax	6
Intrathoracic tumor	6
Extrathoracic tumor	3
Lung abscess	27
Osteomyelitis	2
Abscess in chest wall (sarcoma elsewhere)	1
Tuberculous ribs and pleura	1
Foreign body in the lung	1
Pulmonary tuberculosis (chest wall collapsed)	1
Bronchiectasis or abscess	1
Gunshot wound with empyema	1
Pick's disease	1
Total of 307 diagnoses in 300 cases, in 7 of which there was more than one operative condition.	

Anesthesia

Local or nerve trunk	253
Ether	198
Combined	21
Miscellaneous	26

Type of Operation

Aspiration	244
Rib resection	130
Exploratory operation	30
Aspiration and rib resection	2
Aspiration and cautery	6
Drainage incision	26
Plastic operation	20
Estlander or Schede operation	2
Delorme decortication	5
Decortication (unnamed)	9
Excision of tumor (2 intrathoracic; 2 extrathoracic)	4
Resection of gladiolus (mediastinal sarcoma)	1
Foreign body in the lung	1
Miscellaneous	18

Complications During Operation

Pain	5
Dyspnea or cyanosis	10
Weakness	1
Cough	10
Apnea	1
Expectoration (blood 5; pus 5)	10
Disturbed nervous system	12
Pneumothorax	3
Hemorrhage	2

Convalescence or Termination

Satisfactory	258
Slow or unsatisfactory	13
Superficial emphysema	1
Tuberculosis	2
Cardiac or renal complication	2
Early deaths (within three weeks)	30
Deaths (one to five or more months)	6

312 reports on 300 patients—6 fall under two classifications.

As shown in Table I pneumothorax appeared as a complication following three operations. Two of the patients experienced no difficulty and the third had respiratory embarrassment only until the wound was closed. Thus, with present-day methods of dealing with diseases of the chest, pneumothorax had to be reckoned with but once in 498 operations, and then was only of passing seriousness.

In certain types of operation in which pneumothorax must necessarily be induced, it is advisable to have the lung expanded on closure of the wound, differential pressure might be a decided advantage.

A curious series of symptoms referable chiefly to the central nervous system appeared in 12 patients, consisting of shock, with pallor, failing pulse, poor general condition or restlessness, dilated pupils, deviation of the eyes, and temporary blindness. Temporary paralysis and aphasia have been observed in patients not considered in this series. It has seemed to me that these conditions, especially those affecting the eyes, and producing paralysis or aphasia, have been more common following the use of the cautery than any other method. However, this was not the case in the series quoted.

Whether one believes that the pressure on the two sides of the chest in unilateral open pneumothorax is equal or is not equal, does not detract from Graham's epoch-making experiment. The results of this work are clearly seen in our present-day treatment of thoracic disease, especially of streptococcal empyema. How satisfactory the method has been in the treatment of acute streptococcal empyema has been previously reported by Hedblom. The data I have quoted in Table I refer to patients operated on since Graham pointed out the importance of considering pneumothorax more fully. Operations for pleural infections comprise by far the greatest number of operations on the chest. Open pneumothorax need hardly be considered; the closed method after aspirations is the method of choice. The closed method is not necessary, however, because the delay before using rib resection methods is long enough to allow of the formation of adhesions which prevent marked collapse; the mediastinum and diaphragm are protected and the balance between tidal air and vital capacity is not disturbed. I am referring, of course, to the treatment of streptococcal empyema, not of pneumococcal empyema.

A small proportion of patients require the production of an open pneumothorax. This group includes: (1) traumatized patients; (2) patients with tumors of the chest wall or within the thorax; (3) patients requiring drainage of abscesses in the mediastinum; and (4) patients requiring exploratory operations for diagnostic purposes. In this group conditions within the thorax more nearly approach those on which Graham has based his hypothesis and developed his formula. In the cases comprising this study Lockwood allowed air to enter through a very small opening and proceeded with the operation as soon as the accommodation could be obtained, making an opening sufficiently large to complete the work quickly and easily. By closure of the opening a closed pneumothorax is established on the first signs of danger from disturbed breathing. With a conscious patient co-operation is especially easy and advantageous. Hedblom prefers having a gas-oxygen apparatus at hand so that pressure may be used if there is danger from the

pneumothorax or if it would be advantageous as an alternate method of anesthesia. Artificial pneumothorax induced a few days before operation might be of some advantage, but as yet we have not given the method practical application.

It might be supposed that an opening in the chest wall as large as a cross-section of the trachea would collapse the lung and keep it collapsed. This is not necessarily true. West reports that it is not an uncommon experience on opening the chest for drainage of an empyema cavity to find that the lung, which has been completely collapsed by the effusion, expands as soon as the pus is evacuated. This phenomenon has been observed repeatedly in our own experience. West explains it as follows: "The air in the tubes is not subject simply to atmospheric pressure during the phases of respiration. During inspiration a certain obstruction to the free ingress of air is encountered which produces a subatmospheric pressure in the tubes amounting to 0.5 mm. of mercury. During expiration a similar obstruction to the free egress of air is met producing a pressure of 1.5 to 2 mm. above that of the atmosphere." West believes that these pressure oscillations are sufficient to expand the lung at least one-half and perhaps more, provided it is unhampered by adhesions. In operative work it is impossible to determine whether or not on opening the chest a lung will collapse or be projected through the surgical wound. Lockwood believes there is less danger in an opening large enough to admit the hand than in a small opening. We believe that the benefit of a quiet thorax on the side operated on has not been evaluated sufficiently.

From a clinical study of 50 cases in which there was evidence of pneumothorax we found that they might be classified from an etiologic standpoint (Table II, page 302).

TABLE II

	Cases.
Tuberculosis	28
Empyema (non-tuberculous)	8
Spontaneous (unproved etiology)	6
Bronchial fistula	3
Traumatism	3
Therapeutic	3
Emphysema	2
Thoracentesis	1
Pneumonia (complication)	1
Lymphosarcoma (complication)	1

It will be observed that the cases tabulated total more than 50; two factors were present in some instances and the real cause of the pneumothorax could not be determined. As an example of the overlapping, pneumothorax was induced elsewhere as a therapeutic measure in 3 cases, in 2 of tuberculosis and in 1 of abscess of the lung. Emphysema was claimed to be the cause of the pneumothorax in 2 cases in which other factors were excluded by careful study and in which emphysema was known to be present. Five cases classified as spontaneous pneumothorax fulfilled Hamman's definition, except that in 2 the pneumothorax persisted more than eight weeks. In one of these the history made it seem probable that there had been successive attacks which prolonged the period of absorption. We are of the opinion that an arbitrary time limit as an absolute criterion of diagnosis of spontaneous pneumothorax is unwarranted, and that the findings peculiar to each case can alone determine to which group it should be attributed.

Nineteen cases of simple effusion had been aspirated, elsewhere, on an average of 2.8 times. It is impossible to know how many times aspiration was responsible for air in the pleural space. It must not be assumed that pneumothorax following aspirations is necessarily due to leakage through or around the needle. Puncture of the lung may provide the means for the escape of air, and by remaining patent, produce an open pneumothorax or a valvular type of closed pneumothorax. We witnessed this demonstrated recently. The aspirating needle pierced the lung and at necropsy the lung was collapsed, the rent was found

patent, and promptly emptied the lung after it was inflated. This patient did not succumb from pneumothorax, but from long-continued endocarditis with decompensation. The escape of air through the puncture could be made out readily when the inflated lung was immersed in water. The lung was emphysematous; this result might not have occurred in a normal lung. Unquestionably the lung is punctured by the needle many times without damage. We have repeatedly demonstrated a patent opening in lungs punctured at necropsy, when normal elasticity seemed to have been interfered with.

We consider aspiration in hydropneumothorax to be indicated only for diagnostic purposes or to relieve urgent dyspnea, and then it should be done only by trained men accustomed to the requirements of aseptic surgery. The most serious danger of repeated aspiration aside from that of creating a superadded sudden pneumothorax is the conversion of a hydrothorax or hydropneumothorax into a pyopneumothorax, a sequence that had occurred in 5 of our tuberculous patients before we saw them. Rosenbach believes that two or three aspirations in patients with large amounts of exudate, even when performed with the greatest care, will almost certainly produce putrefaction and lead to rapid loss of strength. Added to this danger is the risk of the formation of fistulæ at the site of the aspirations, a sequence appearing in one of our tuberculous patients.

One type of case only seems to require communication with the outside. One of our patients was seized with symptoms of urgent dyspnea following an operation for the removal of the lacrimal sac, and death followed in five hours under expectant treatment. A previous careful examination had not revealed evidence of pulmonary disease and the case was classified as spontaneous pneumothorax. We believe that expectant treatment is insufficient in the urgent cases. Paracentesis should be tried. This view is supported by Fussel and Riesman, Meyer, Lord, Rosenbach, Findlay, and Weber. Lord and especially Rosenbach prefer using conservative methods first. West uses a fine trocar or needle to which he attaches a rubber tube, the latter being allowed to remain under sterile water. In

reference to the danger of reopening the perforation in the lung Findlay aptly remarks, "It is better to run the risk than to allow the patient to die of asphyxia."

CONCLUSIONS

1. The danger of open pneumothorax is reduced to a minimum by the present methods of treating empyema, especially if of streptococcal origin.

2. Local or paravertebral anesthesia during operation is the method of choice; it possesses many advantages to the surgeon and adds to the safety of the patient.

3. It is our experience that differential pressure is of advantage in a relatively small percentage of operations.

4. The size of the opening to be made in the wall of the chest is determined by the requirements of the surgeon because the mediastinum is rarely completely unsupported by adhesions.

5. The behavior of the lung cannot always be foreseen.

6. Certain forms of spontaneous pneumothorax may require surgical intervention.

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PRIMARY CANCER OF THE LUNG FROM THE ROENTGENOLOGIC VIEWPOINT

RUSSELL D. CARMAN

PRIMARY cancer of the lung, although relatively infrequent, occurs sufficiently often to make its diagnosis a subject of considerable importance.

Krause cites Hesse as having found 99 cases of primary pulmonary carcinoma in 63,088 necropsies. Von Wiczkowski compiled reports of 58,497 necropsies with 125 primary cancers of the lung. These statistics and those of Adler and others indicate an incidence of 0.15 per cent. or more of all necropsies, 1 per cent. or more of all cancers, and over 2 per cent. of all deaths from pulmonary disease.

SYMPTOMS

Clinically, the symptoms vary in emphasis and, as Adler says, in many cases the diagnosis is impossible because there are no symptoms pointing to the lungs. In many instances with pronounced manifestations a diagnosis of tuberculosis is made, and, according to Scott and Forman, Swan, and others this is a common error.

Cottin, Cramer and Saloz, reporting 29 cases observed at the cantonal hospital at Geneva, state that in only 6 cases was the condition recognized during life. Cases erroneously diagnosed fell into two groups: those mistaken for mediastinal tumor, bronchopneumonia, gangrene, tuberculosis, cyst or empyema, and those in which the pulmonary tumor was latent and symptoms of extrathoracic metastasis (brain, liver, or spinal cord) were dominant.

The salient symptoms recorded include dyspnea, cough, pain, hemoptysis, fever, and cachexia, all varying in degree and combination. Dyspnea ranges in severity from a slight short-

ness of breath on exertion to harassing orthopnea; although frequently a symptom, it may be totally absent. Cough is perhaps most common of all; in the early stages it is likely to be constant, although not distressing, and dry; later it may become severe and accompanied by purulent or sanguinolent expectoration. Pain is dependent largely on pleural involvement, and varies from mere discomfort to a stabbing pain. Bloody expectoration is likely to occur at some period of the development of most pulmonary tumors, and a profuse hemoptysis may be the first symptom. Fever has been reported in many cases, but in the absence of complications there is usually no marked rise of temperature. Cachexia occurs irregularly, often late (Packard), and may be completely lacking; some patients maintain good color and weight, and a few even gain in weight.

Obviously, the symptoms may be quite eccentric in degree and in association with each other, and, while purely clinical antemortem diagnoses have sometimes been made, the majority have been determined after death. In later years the Roentgen-ray examination has been employed with advantage. In this paper attention will be directed to the various phenomena observed roentgenologically.

Since the changes in the roentgenologic pictures on which all Roentgen-ray diagnoses are based are directly dependent on the situation, extent, and character of the pathologic alterations present, the observations of the pathologists in pulmonary malignancy are of fundamental importance.

PATHOLOGIC ANATOMY

Adami and Nicholls state that primary cancer of the lung generally affects, by preference, the right side, and is either nodular or diffuse, that there are three main types in which the new growth starts from the bronchi, or the bronchial mucous glands, or the alveolar epithelium, and that the tumors readily soften so that they are not unlike caseous tuberculous masses, and cavities may result from a discharge of this material into a bronchus.

The American Text-book of Pathology[11] notes that secondary peribronchial and interlobular nodules may surround the primary growth. The primary nodes form uneven nodular papillary growths. Portions may break off and be inspired to deeper parts of the bronchial tubes, producing secondary masses. In some instances the neoplasm forms large solitary nodes which spread peripherally, affecting air-cell after air-cell, and stuffing the lymphatics with cell-nests in its progress.

Kaufmann describes three forms of primary cancer of the lung:

1. A tumor beginning in the first or second branch of a main bronchus, near the hilus. This may result in a circumscribed stenosing infiltration, or a large nodule surrounding the bronchus, or thick string-like infiltrations extending out from the hilus along the lymph-vessels, or a carcinomatous lymphangitis develops, with the greater and lesser lymph-channels filled clear out to the alveoli.

2. An infiltrating form in which sometimes an entire lobe is infiltrated with caseous, pneumonic, carcinomatous material.

3. A circumscribed tumor in the midst of a lobe, soft or hard, more or less round, and of varying extent. There may be nodular foci in its vicinity and eventually in the other lobes of both sides.

Aschoff speaks of two types, one arising from a bronchus of the first to the third order, the other, the infiltrating type, in which large portions of the lung, or an entire lobe, may be filled with grayish-white or yellowish masses which have no sharply marked limits and whose origin is hard to determine. He notes that in many cases cancers of the lung are small and are not diagnosed *intra vitam;* death occurs from metastasis (to the brain, for example), and the clinical symptoms are only those of the metastasis.

Ribbert says that carcinoma of the lung usually arises in the wall of a bronchus, especially of the lower lobes, and is situated toward the hilus. The bronchial lumen may be narrowed by thickening of its wall or broadened by ulceration. The tumor is seen commonly as a grayish-white mass "from the

size of an egg to that of a fist." It sometimes infiltrates an entire lobe with a pneumonia-like thickening. There may be secondary nodules in the other lung. The bronchial, mediastinal, and supraclavicular glands become carcinomatous. In a special histologic form the cancer occurs as polypi springing into the lumen of a bronchus.

Weller collected 88 cases and added 1 of his own. He hoped that an analysis of a large number of cases of primary bronchial cancer would aid in forming a definite clinical picture of this condition and take it out of the mixed group of bronchial and pulmonary cancers with which it is usually considered. Contrary to the current view, Weller found the right and left sides to be involved with equal frequency. He also notes a proneness to metastasis in the brain (12 cases).

Pässler in 70 cases of cancer of the lung found 47 (nearly 70 per cent.) in which the lesion was probably primary in the bronchus.

Orth states that, histologically, some of the cancers are cylinder celled or adenomatous, or, more commonly, small celled and polymorphous; others show typical cancroid structure. The former may be regarded as arising from the bronchi, the latter either from alveolar epithelium or from metaplastic or existing flat epithelium in the bronchi. Frequently cancroid is observed in tuberculous cavities.

Delafield and Prudden note the association of cancer with exudative pneumonia involving large portions of the lung as well as the pleura.

Adler's monograph with 374 collected cases and his illuminative comments thereon gives a careful analysis of the pathologic conditions found. He notes that the gross appearance is not uniform or characteristic. One form, which occurs very rarely, is that of a single nodule, usually quite small, surrounded by a few minute miliary nodules, deeply buried in the tissue of one lobe of the lung, producing slight symptoms or none. A miliary form described by Wolff, Rokitansky, and Elisberg, resembling miliary tuberculosis save that the small nodules are larger than the tubercles, Adler believes to exist, but he

thinks these cases are not always primary. A third form, the multiple nodular type, as a rule involves at the beginning only a portion of one lung; the nodules vary in size "from that of a cherry pit to that of a fist," with sharply defined boundaries and are not usually confluent. An infiltrating tumor, starting from a bronchus, is very common. It infiltrates the lung along the ramifications of the bronchus as well as of the veins, arteries, lymphatics, and even nerves. Another form of infiltrating tumor starts from a smaller bronchus or bronchiole, affects only a portion of a lobe, and is very dense.

Since Adler's cases were collected from many sources, details are often incomplete, but a survey of the necropsy findings reveals many interesting facts.

One hundred and eighty-eight of the cancers were in the right lung and 157 were in the left. The most extensive pathologic change, as directly stated or to be inferred from the description, was in the upper lobe in 91 cases, in the hilar region in 90, and in the lower lobe in 75. While the right middle lobe was often implicated in conjunction with either the upper or lower, it was involved alone in but 15 cases. Practically an entire lung was affected in 48 cases, and extensive invasion of both lungs was recorded in 16. In only 6 instances was apical involvement noted. Miliary lesions were observed in 6 cases. Metastatic nodules in other parts of the same lung or in the opposite lung were recorded in 60 cases. Involvement of the pleura was reported in 66 cases, and fluid of varying amount was noted in 46. However, Adler makes the statement that in nearly every case of lung tumor the pleura participates to a certain extent in the morbid process. In about half the cases involvement of the bronchial or mediastinal lymph-nodes was specifically mentioned. Cavities, small or large, single or multiple, in the carcinomatous tissue were observed in 60 cases, though in numerous instances these were filled with necrotic material.

Many complicating factors which would materially affect the Roentgen-ray picture become apparent on studying these reports. Thus, in 75 cases the large vessels in the mediastinum

were either invaded directly or compressed by the tumor mass. Bronchiectasis was recorded in no less than 28 cases; 19 cases were either probably or definitely associated with tuberculosis; a few showed tuberculous cavities, and in 3 the miliary form of tuberculosis was noted. Atelectasis from bronchial obstruction or compression was mentioned in several cases; in a few instances pneumonias of various types were present. Of more general interest is the fact that metastasis to the brain was found in 38 cases, and in 11 others the dura or cranial bones were affected. Secondary lesions of the liver, kidneys, spleen, bones, or other organs were, of course, noted in a large number of cases. More than 70 per cent. of all the cases occurred in males.

Regarding the Roentgen-ray examination Adler says: "It has repeatedly been noted that in lung tumor the mobility of the lung is markedly diminished or entirely abolished. In cases of mediastinal tumor the respiratory mobility of the lung remains unchanged or is increased, and Jacobson has found this valuable in distinguishing between the two types of tumor. . . . The shadow of a carcinoma or sarcoma just starting from the hilus and gradually extending toward one of the pulmonary lobes is a very striking picture, and often suggests the tumor diagnosis when the observer, though other characteristic symptoms were present, would have been led astray. The interpretation is more difficult when the shadow extends over the upper lobe of either side, as this is the favorite localization of tuberculous processes. Sometimes the sharp linear delimitation at the base of the shadow makes for tumor rather than tuberculosis. It speaks for tumor also if the affection is confined to one upper lobe. . . . But where tuberculosis is associated with advancing carcinoma or sarcoma the Roentgen rays are of little value, and if a differential diagnosis is possible, it must be attempted by other means."

ROENTGENOLOGIC FEATURES

Among the roentgenologists who have given painstaking descriptions of the disease are Arnsperger, Groedel, Otten, Assmann, Barjon, Jaugeas, Holmes and Ruggles, and Christie.

Arnsperger has noted two roentgenologic forms, the carcinomas which extend from the hilus with streak-like extensions into the adjacent lung field, or those in which the surrounding field is sown with small areas, corresponding to Otten's variety involving the parenchyma of a lobe. In the first form there is an intense shadow with a convex border extending into the lung, and with prong-like projections from the border, or numerous small shadows around it. The small spots are not clear cut, and are most distinct in the direction of the hilus ramifications. These tumors are mostly bronchial carcinomas which begin in the hilar region and go out along the bronchi. The areas broaden in all directions and progressively involve the entire lung or only a single lobe, giving a picture like that of tuberculosis. It contrasts with the uniform solid tumors such as sarcoma. When the mediastinal glands are involved it is often hard to determine whether the original growth was in the lung or in the mediastinum.

Krause, discussing all lung tumors, classifies them in three roentgenologic groups: (1) Tumors which extend as an arch from the hilus shadow. Of this sort are the carcinomas, which originate in or around the main bronchus near the tracheal bifurcation. (2) Tumors which infiltrate a lobe. These show as large, dense shadows sharply set off from the clear lung. A sarcoma of the upper lobe, which Krause saw, exemplified this class. (3) Small tumors in the medial lung field. To these belong the connective-tissue tumors, such as fibromas, osteomas, chondrolipomas, and enchondromas.

Jaugeas finds that carcinoma is located either at the hilus or in a lobe. Hilar cancer gives an intense shadow with radiations from its convex border. Lobar cancer sometimes overshadows almost an entire lung, leaving clear areas only at the apex and base. The signs are not characteristic, for they are seen in various other affections. Primary sarcoma of the mediastinum is distinguished by its clean contour and rounded form.

Assmann points out that the Roentgen-ray shadows of tumors are not only due to the tumor tissue itself but also to numerous complicating factors, especially to neighboring infil-

trative processes, atelectasis due to compression of a bronchus, connective-tissue formation, and shrinking processes. Often there is gangrenous disintegration of tissue or abscess formation or pleural exudates which may completely change the original character of the Roentgen-ray picture. He cites 2 cases of primary cancer, confirmed by necropsy, both of which showed dense semicircular shadows in the hilum with radiations therefrom. In each instance the cancer originated in the right bronchus. He also had a case in which there was a tumor of the right upper lobe, filling the entire upper field and having a sharp, horizontal lower border. Shrinking processes and impeded diaphragmatic movement on the affected side were also noted. It could not be distinguished roentgenologically from a postpneumonic carnification.

Holmes and Ruggles state that primary cancer is practically always unilateral and occurs in two types, nodular and infiltrating. The former consists of dense, rounded masses, occurring near the hilus, and sharply marked off from the lung tissue. In the infiltrating type the tumor arises from a bronchus, infiltrates the lung along the bronchial ramifications, and gives an increase in density of the lung markings, or it may involve surrounding lung tissue and be seen as a mass with fairly smooth edges except the advancing margin, which is irregular. Collapse of the lung may cause displacement of the heart to the affected side. Fluid in the pleural space occurs early.

Barjon recognizes cancer of the lobe and cancer of the hilus. The former is characterized by an extensive shadow occupying an entire lobe, preferably an upper, and resembling a frank pneumonia, though less opaque and less homogeneous. In the only case of cancer of the hilus which he saw the left lung was congenitally deformed; the two lobes were divided not by a lateral fissure, but by a longitudinal fissure, and the cancer was confined to the hilar lobe.

Christie, from the roentgenologic point of view, mentions an infiltrative type, a miliary type, and findings which are not typical. He designates as the infiltrative type that originating in a large bronchus with a roughly circular shadow shading

off into the lung and with radiating processes. Beyond this is a less dense shadow zone caused by congestion and atelectasis. If there are also some small indistinct, outlying nodules, Christie considers the picture characteristic. Diffuse nodules, with hazy peripheries, throughout the lungs are seen in the miliary type.

Ten cases of primary malignancy of the lung and pleura have been observed by Engelbach and Schnoebelen. The lesions included carcinoma and sarcoma of the lung and endothelioma of the pleura. Several illustrative roentgenograms are presented. The writers assert that the majority of malignancies occur primarily in the mediastinum and invade the upper lobes of the lungs, more frequently the right. In the absence of pleural involvement the Roentgen-ray shadow of the tumor is evenly dense, not confined to lobar boundaries, and its progressive infiltrative growth, as shown by successive examinations, furnishes very positive diagnostic information.

Otten reports 13 cases of primary cancer all examined *intra vitam* by the Roentgen ray and proved by necropsy: 11 were in men; 2 were in women. In 7 cases the right lung was involved; in 6 the left. An upper lobe was invaded in 9 cases, 3 in conjunction with the right middle lobe. Bronchial origin of the growth was determined in 9 of the cases. Implication of the hilar and bronchial lymph-nodes was found in 9. From a roentgenologic viewpoint Otten distinguishes two main groups besides a minority of cases which were either intermediate between the groups or could hardly be classified. In the first group (6 cases) the tumor arose from a large or main bronchus and spread out over one or two lobes, transforming them into a compact mass. Accordingly the lobar shadow dominated the Roentgen-ray picture; the shadow was dense, usually homogeneous, rather sharply delimited, and extended from the hilus to the thoracic wall. Although an upper lobe was involved in most of this group, a striking feature was the comparative exemption of the apices, which even when implicated remained somewhat translucent. In the second group of 3 cases the new growth followed the bronchial tree outward from the root

of the lung, infiltrating the tissues, but not involving any large lobar area. In this group the chief Roentgen feature was the shadow in the hilar region, fairly dense, but not homogeneous, and becoming thinner peripherally. The remaining 4 cases were somewhat different and Otten does not classify them in the second group, but the lesions were largely hilar, with peripheral shading off. Otten points out the difficulties attending the Roentgen diagnosis of this condition, and, although the Roentgen ray is of vast assistance and may supply determining evidence, it should be used, he insists, only as an adjunct to the clinical examination.

McMahon and I, in reporting 5 cases from the Clinic about four years ago, classified them roentgenologically in three types—infiltrative,[1] miliary, and mixed. The term "infiltrative" was applied to those showing massive shadow areas, "miliary" to the small shadows scattered through both lungs, and "mixed" to combinations of large and small shadows. One of the cases classified as miliary was proved at necropsy to be carcinoma, with no evidence of a primary growth elsewhere. Thus the type seemed to be warranted roentgenologically, as the miliary shadows dominated the roentgenograms.

TECHNIC

Stereoscopic plates are essential to satisfactory examination of the chest. These may be made with the patient standing, sitting, or prone; in our work we prefer the standing position. Roentgenoscopy is an important supplement to roentgenography, especially in those cases in which the mediastinum is invaded, in order to distinguish between cancer at the root of the lung and aneurysm or other mediastinal lesions. It is especially valuable in determining the presence or absence of pleural effusions. Fluoroscopy permits inspection of thoracic

[1] While the term "to infiltrate" and its derivatives have a rather definite meaning to the pathologist, they are often applied to diverse types of roentgenologic shadows, and thus tend to give confusing impressions. Further, the roentgenologic appearance cannot determine whether a lesion is an infiltration or a process of some other character. It seems advisable, therefore, to abandon the term in the description of phenomena in the roentgenogram.

conditions at any desired angle of view, as well as their behavior during various phases of respiration. In this connection Adler's remarks, above quoted, regarding the different effect of pulmonary and mediastinal tumors on the respiratory mobility of the lung are well worth remembering. In doubtful cases reexamination at intervals will show the rate of growth of the lesion and assist in determining its probable character.

AUTHOR'S SERIES

In Tables I, II, and III are presented the essential features of 37 cases. The material was classified and tabulated by Dr. Charles H. Heacock of the Mayo Foundation; 28 of the cases are from the Mayo Clinic. Nine were obtained, at the suggestion of Dr. H. E. Robertson, from the records of the Department of Pathology of the University of Minnesota; for the roentgenograms of these I am indebted to Dr. R. G. Allison, Roentgenologist of the University Hospital (3 cases), Dr. K. Ikeda, Roentgenologist of the Minneapolis General Hospital (4 cases), and to Dr. C. W. Pettit and Dr. H. B. Sweetser of Minneapolis (1 case each).

Seventeen of the 37 cases were verified by necropsy (Table I). Biopsy was made in 10 cases; in 7 of these cancer was found in the tissue examined (Table II). Ten cases are supported by clinical and roentgenologic evidence which was considered reasonably diagnostic (Table III).

Roentgen-ray findings in each case are noted in the appropriate column of the tables. A comparison of the necropsy reports with the Roentgen-ray findings in this series will occasionally show apparent or real discrepancies. The necropsy findings must be accepted by the roentgenologist, and he cannot hope to understand the Roentgen-ray picture without some knowledge of them, but he may often note considerable differences between his observations and those of the pathologist. Unless the necropsy report is unusually profuse in details, factors which materially affect the Roentgen-ray picture, such as circulatory stasis, atelectasis, pneumonic infiltration, etc., may not be recorded by the pathologist, whose attention is

TABLE I

CARCINOMA OF THE LUNG PROVED BY NECROPSY

Case. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Necropsy findings.	Remarks.
1917—214[1] M. 55	One year; loss of weight; edema of face; cough with expectoration; dyspnea; pain.	Dilatation of veins of face; signs of consolidation on right side.	Absolute density throughout right lung; massive shadow fairly well circumscribed in left lung; increased density over diaphragm on left side. Diagnosis: Carcinoma.	250 c.c. fluid in pocket between right lobe and pericardium; nodular tumor of right upper lobe with extension to superior vena cava. Metastasis to left upper and lower lobes just above diaphragm. Diagnosis: Primary carcinoma of right upper lobe.	Biopsy: Axillary gland inflammatory.
1919—35[1] F. 58	Progressive weight loss; cough; hoarseness; dyspnea; hemoptysis; pain.	No record.	Retration of left chest with compensatory emphysema on right side; a uniformly dense, sharply outlined shadow extending outward and downward from left hilar region; increased bronchial markings on right side.	Left lower lobe thickly studded with irregular white nodules; slight necrosis in some areas; metastasis to right lung, left pleura, liver, suprarenals, kidneys, and mediastinal glands. Diagnosis: Adenocarcinoma of left lower lobe.	
1920—363[1] M. 46	One year; weight loss 30 pounds in two months; cough; dyspnea; hemoptysis; elevation in temperature.	Flaccid paralysis of left arm; dulness with absence of breath sounds over left chest.	Increased density throughout left chest, marked in upper third, through which the ribs were seen; apex translucent; right lung negative; heart displaced to left.	800 c.c. fluid in left pleural cavity and 1500 c.c. in pericardial sac; pleura thickened; left lung collapsed; tumor mass occluding left bronchus and extending into lung; metastasis to brain, dura, and right suprarenal. Diagnosis: Primary carcinoma originating in left bronchus.	

[1]From the University of Minnesota.

Case. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Necropsy findings.	Remarks.
1920—396[1] M. 72	Headache.	Crepitant râles over right base; diminished fremitus and breath sounds on left side posteriorly.	Solid shadow throughout right lung, slight increase in density in the left lung; heart displaced to right.	Large nodule in right lower lobe with smaller scattered nodules in both lungs; careful search revealed no primary lesion elsewhere; metastatic nodules in liver. Diagnosis: Primary carcinoma originating in right lower lobe.	No symptoms referable to chest; careful search for primary tumor elsewhere negative.
1921—8[1] F. 62	Cough; dyspnea; pleuritic pain on left side.	No record.	First examination: Rather uniformly dense circumscribed shadow extending outward from left hilum, half-way to chest wall; right lung negative save for calcified areas at hilum. Second examination: Shadow increased about one-third in size, with veiling of left upper lobe.	Tumor originating in and obstructing left upper bronchus extending into left upper lobe and almost completely occupying it; areas of cystic degeneration, metastasis to right lung, cervical glands, thyroid, and ribs. Diagnosis: Primary carcinoma of left upper lobe.	
1921—147[1] M. 49	Two years; weight loss 50 pounds; severe cough; dyspnea; marked hemoptysis.	Emaciation; signs of consolidation in right upper chest.	1/5/21: Solid circumscribed shadows involving part of right upper lobe, apparently in contact with mediastinum. 2/17/21: Shadow largely disappeared, leaving heavy radiating lines suggesting fibroid tuberculosis; markings in left lung somewhat intensified. 3/17/21: Findings similar to those noted at first examination, but shadow less circumscribed; probably primary carcinoma.	Partial obliteration of pleural cavities and acute pleuritis; mass obstructing right bronchus, and extending into right upper lobe; partial atelectasis; pneumonia of right upper and middle lobes; many bronchiectatic cavities filled with pus; metastasis to the liver, kidney, and thyroid. Diagnosis: Primary carcinoma originating in right bronchus.	

[1] From the University of Minnesota.

TABLE I (continued)

Case. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Necropsy findings.	Remarks.
Case 1921—147 continued			3/24/21: Shadow increased in size so as to involve upper right and middle lobes. Diagnosis: Lobar pneumonia of right upper and middle lobes.		
1921—191[1] M. 63	Three months; marked cough; marked dyspnea.	No record.	Mottled density of entire right upper lobe, blending with median shadow; otherwise lungs and heart negative.	300 c.c. fluid in right side; tumor mass involving entire right upper lobe with extension into posterior mediastinum and pericardium; central areas of necrosis; metastasis to right lower lobe, liver, and kidneys. Diagnosis: Primary carcinoma of right upper lobe.	
1921—216[1] M. 60	One year; cough; dyspnea; pain.	No record.	Dense shadow not sharply bordered extending upward and outward from left hilum; lung markings about hilum somewhat intensified.	Effusion of 500 c.c. in both sides; tumor mass originating in and occluding left main bronchus and extending into left upper lobe; epicardium involved; areas of necrosis; metastasis to left lower lobe, pleura, ribs, spleen, kidneys, suprarenals, and lymph-nodes. Diagnosis: Primary adenocarcinoma arising from bronchus.	
1921—239[1] M. 46	Three years; pain in the back.	Knuckle deformity of twelfth thoracic vertebra; paraplegia; dullness over right	6/2/21: Chest, hilar markings exaggerated on both sides; apices clear. 6/2/21: Spine, metastasis	Irregular plaque in left bronchus; lung, parenchyma not invaded; metastasis to kidney, duodenum,	Case clinically diagnosed Pott's disease repeatedly.

[1] From the University of Minnesota.

Case. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Necropsy findings.	Remarks.
Case 1921—239[1] continued		chest, with distant breath sounds.	to twelfth thoracic vertebra.	twelfth thoracic vertebra, and spinal cord. Diagnosis: Primary carcinoma of left bronchus.	Biopsy: Inguinal gland inflammatory.
95,595 M. 44	One year; weight loss 50 pounds; cough; dyspnea; hemoptysis; pain.	Dullness and absence of breath sounds over left upper chest; râles over left base.	Large circumscribed shadow projecting outward and upward from left hilum; just above this shadow a well-circumscribed shadow about 2 cm. in diameter, and in fifth right interspace, near spine, a smaller shadow.	Pericardial effusion; tumor of left upper lobe apparently originating in bronchus; metastasis to right lung. Diagnosis: Primary carcinoma of left upper lobe.	Necropsy performed at patient's home.
109,685 M. 58	Four months; occasional cough; progressive dyspnea.	Moist râles over both sides.	Multiple miliary shadows of increased density throughout both lungs.	400 c.c. of hemorrhagic effusion in left pleural cavity; lungs congested and infiltrated throughout with dense white bands; primary focus within or without the chest not demonstrated. Diagnosis: Primary carcinoma of the lungs.	
158,374 M. 57	Two years; weight loss 35 pounds; severe cough; marked dyspnea; hemoptysis on three occasions; substernal pain.	Signs of consolidation in right lower lobe.	Large circumscribed shadow involving right lower lobe, projecting above curved fluid line of Damoiseau; heart shadow displaced to the left.	Marked effusion in right side; tumor of right lower lobe with extensive central necrosis. Diagnosis: Primary carcinoma of right lower lobe	Microscopic diagnosis made by Dr. J. J. McKenzie, of Toronto.
159,177 F. 47	Seven months; weight loss 20 pounds; cough; marked dyspnea.	Dullness on both sides; râles over both bases.	Translucent shadow involving entire right upper lobe except the apex; miliary shadows of metastatic areas throughout lungs.	Primary carcinoma of lung without extrapulmonary metastasis.	Patient died at home, where necropsy was performed.

TABLE I (continued)

Case. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Necropsy findings.	Remarks.
160,751 M. 61	Seven months; weight loss 15 pounds; cough; dyspnea.	Tumor of right side of neck; dulness throughout chest, exaggerated voice sounds.	Dense shadow involving right middle lobe; extensive shadows indicative of metastasis to lungs, except apices; apices quite clear.	Effusion on right side; tumor involving all lobes of right lung; areas of necrosis. Diagnosis: Primary carcinoma.	Only thorax examined at necropsy.
195,980 M. 58	Four months; weight loss 40 pounds; cough; dyspnea; slight elevation of temperature; pleuritic pain.	Signs of effusion at right base.	Increased density in right base, probably fluid; miliary shadows of metastatic areas throughout lungs.	Adenocarcinoma of lungs; metastasis to liver.	Pleural effusion tapped twice. Necropsy performed at patient's home.
280,176 M. 42	Nine months; weight loss 30 pounds; cough; dyspnea; slight elevation of temperature.	Signs of fluid in right chest.	Irregular shadow with radiating margins extending outward from right hilum; pleurisy between right middle and lower lobes.	300 c.c. fluid in pleural cavity; tumor in base of right lower lobe; metastasis to left lung; pleura, bronchial and mesenteric lymph-glands, and liver. Diagnosis: Primary carcinoma arising from cells lining the alveoli.	
328,955 F. 17	Four months; weight loss 20 pounds; severe cough; dyspnea.	Tumor of upper sternum; dullness and diminished breath sounds on left side.	Large, homogeneous, dense, circumscribed shadow extending from left hilum almost to periphery; smaller shadow projecting from right hilum half-way to periphery; apices clear.	100 c.c. fluid in right side; atelectasis of left lung; left chest almost filled with huge tumor apparently originating in left hilus; three large cavities containing fluid; invasion of posterior mediastinum; metastasis to right lung, pleura, and spine. Diagnosis: Primary carcinoma, probably originating in left bronchus.	

TABLE II

CARCINOMA OF THE LUNG WITH BIOPSY EXAMINATION

Case. Date. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Biopsy findings.	Clinical diagnosis.	Remarks.
176,118 10/24/16 M. 35	Eight months; weight loss 16 pounds; slight cough; choking sensation; dyspnea; hemoptysis once.	Immobility, dulness, diminished breath sounds, and increased fremitus over right chest.	Markedly increased density of right lower lobe; hilar shadow intensified.	11/3/16: Specimen from right lung and pleura; carcinoma.	Primary carcinoma of lung.	Bacillus tuberculosis not demonstrated in sputum 12/6/16; follow-up letter unanswered.
229,815 4/29/18 M. 66	Sixteen months; marked loss of weight; nonproductive cough; dyspnea; weakness; 0.5 degree elevation of temperature.	Slight dullness with areas of hyperresonance and harsh breath sounds on left side; harsh breath sounds and limited expansion on right side.	Large round circumscribed shadow in right lower lobe.	2/25/18: Tissue from right lung (at operation); neoplasia, necrosis too extensive for diagnosis of character of growth.	Abscess (?) and malignancy of right lung.	Reports of Roentgen findings during treatment by Dr. Marty of Kansas City: 6/28/18 shadow larger. 7/11/18 appreciable diminution. 8/1/18 not much change. 10/8/18 death; necropsy not performed.
237,004 7/8/18 M. 56	3.5 months; weight loss 20 pounds; cough; expectoration; dyspnea; abdominal pain.	Râles throughout lungs; bronchial breathing on right anteriorly and in right axilla.	Extensive shadow with irregular margin extending from right hilum in all directions, especially downward; apices clear.	7/13/18: Supraclavicular gland: carcinoma.	Primary carcinoma of lung.	Death (respiratory) two weeks after patient left Clinic; necropsy not performed.
270,910 5/14/19 M. 47	Eleven months; cough; dyspnea; pain in left shoulder.	Puffiness of face; dilation of left jugular vein; left chest flat; sonorous râles throughout lungs with prolonged expiration.	Large, dense, well-rounded shadow with circumscribed margin extending outward from left hilum, reaching lateral chest wall; apices clear.	5/19/19: Biopsy, supraclavicular gland inflammatory.	Tumor of left lung.	5/20/19 puncture of left chest with needle without result. 6/10/20 death.
282,455 7/30/19 M. 36	Ten months; weight loss 27 pounds; severe cough; dyspnea; hemoptysis twice; sputum	Distention of superficial veins of neck, chest, and arms; marked dulness over right	Large shadow with circumscribed margin projecting from upper mediastinum to right;	8/2/19 biopsy: Supraclavicular gland inflammatory.	Mediastinal tumor.	Bacillus tuberculosis not demonstrated in sputum.

TABLE II (continued)

Case. Date. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Biopsy findings.	Clinical diagnosis.	Remarks.
Case 282,455 continued	generally blood-tinged; pain; weakness.	apex, but no râles; breath sounds trifle weak.	two nodular shadows just below and lateral to large shadow; apices clear.			
288,486 9/9/19 M. 60	Ten months; weight loss 37 pounds; cough; dyspnea; slight hemoptysis; pain; weakness.	Signs of consolidation in right lower lobe.	Extensive shadow with irregular margin extending from right hilum in all directions, especially upward; similar shadow, but much less extensive on right; apices clear.	9/11/19 supraclavular gland: carcinoma.	Indeterminate.	
296,247 11/11/19 M. 46	One year; weight loss 38 pounds; marked cough; marked dyspnea; pain in right chest; elevation in temperature.	Signs of consolidation in right lower lobe.	Large shadow with radiating margin projecting from right hilum; shadow in region of left hilum; apices clear.	11/14/19 supraclavicular gland: carcinoma.	Carcinoma of lung.	12/4/19 death; necropsy not performed; severe pain; dyspnea; tachycardia and arrhythmia before death.
310,087 3/25/20 M. 56	Four months; weight loss 8 pounds; cough; dyspnea; pain along left costal margin.	Signs of consolidation in left lower lobe.	Large shadow extending outward from left hilum; fluid at left base; increased density at left apex; right apex clear; nodular shadows of metastatic areas in right lung.	3/29/20 supraclavicular gland: carcinoma.	Malignancy of left lung.	
334,970 9/22/20 M. 57	Fifteen months; weight loss 90 pounds; severe cough; dyspnea; evening elevation of temperature.	Tumor of scalp of three months' duration. Signs of fluid at base of left lung.	Shadow in left hilum; fluid at left base; apices clear.	9/27/20: Tumor of scalp; basal-cell epithelioma.	Probably neoplasm of left lung.	Wassermann reaction positive. 1/4/21 death; necropsy was not performed; 1500 c.c. of almost pure blood removed from pleural cavity by undertaker. Roentgen-ray reports from Dr. T. A. Groover of Washington, D. C.:

Case. Date. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Biopsy findings.	Clinical diagnosis.	Remarks.
Case 334, 970 continued						7/8/20 large shadow extending outward from left hilum. 8/6/20 small amount of pleural effusion. Diagnosis: Primary carcinoma of lung originating at hilum.
355,483 4/15/21 M. 58	One year; weight loss 30 pounds; cough; hoarseness; dyspnea; pain in left chest.	General lack of expansion with diminished resonance and fremitus; feeble breath sounds; cervical glands enlarged.	Innumerable miliary shadows in lungs, especially right; left apex clear; right apex involved.	4/21/21 supraclavicular gland: carcinoma	Indeterminate.	

TABLE III
CARCINOMA OF THE LUNG DIAGNOSED ON CLINICAL AND ROENTGEN-RAY EVIDENCE

Case. Date. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Clinical diagnosis.	Remarks.
124,233 2/10/15 F. 44	Eighteen months; marked loss of weight; cough; marked dyspnea.	Dullness over both upper lobes; pleural effusion at left base (2000 c.c. aspirated).	Dense, scalloped, circumscribed shadow extending from right hilum and involving right upper lobe; shadow in right apex; shadow projecting from left hilum; fluid in left base; left apex clear.	Tumor of lung.	Patient also had goiter. Death six months after patient left Clinic. Report from home physician: "No question about correctness of diagnosis of carcinoma of lungs."
124,893 2/20/15 M. 51	Eight months; weight loss 28 pounds; cough; dyspnea upon exertion; hemoptysis once; weakness.	Signs of fluid at right base.	2/20/15 dense shadow in right middle lobe. 4/8/15 right chest filled with fluid to level of third rib. 4/11/15 (after tapping) shadow much larger.	Carcinoma of lung; secondary anemia.	7/24/15 death; course of disease suggested primary carcinoma of lung.

TABLE III (continued)

Case. Date. Sex. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Clinical diagnosis.	Remarks.
138,757 8/16/15 F. 35	Twenty-two months; weight loss 35 pounds; cough; dyspnea; substernal pain.	Dilatation of all superficial veins; general adenopathy; swelling of ankles and knees; indefinite abdominal masses; ascites (1); signs of consolidation in left upper lobe.	Dense shadow involving left upper lobe; shadow representing metastasis to lungs; apices clear.	Primary tumor of lung.	Death soon after patient left Clinic.
189,502 3/26/17 M. 39	Cough; dyspnea; hemoptysis once five years before, several times one year before.	Dullness and distant breath sounds over left lower axilla; occasional râle at right base.	Fairly dense shadow with moderately circumscribed margin projecting from left hilum outward and downward; linear markings on right somewhat exaggerated; apices clear.	Indeterminate.	Bacillus tuberculosis not demonstrated in sputum.
197,196 6/12/17 M. 62	Ten months; weight loss 30 pounds; cough; dyspnea; weakness.	Emaciation; widening of mediastinal area of dulness; heart enlarged to left.	Mediastinal shadow suggesting malignancy.	Primary carcinoma of lung.	Death apparently from pulmonary malignancy a few weeks after patient left Clinic.
199/262 7/2/17 M. 61	One year; weight loss 30 pounds; cough; dyspnea; hemoptysis; pain on movement of left arm.	Dullness over right base; diffuse shower of high-pitched râles after coughing.	Shadow of great density with irregular borders extending outward and downward from right hilum; density at left hilum; somewhat exaggerated; apices clear.	Malignancy of right lung.	
204,866 8/15/17 M. 47	One year; weight loss 20 pounds; very severe cough; hoarseness; dyspnea; marked hemoptysis; severe pain in left chest and back.	Dullness and râles throughout, but most marked over right upper lobe anteriorly.	Shadow in both lungs, probably of malignant tumor.	Tumor of both lungs, probably primary carcinoma.	Bacillus tuberculosis not demonstrated in sputum. Death five months after patient left clinic; necropsy not performed. Signs of general carcinomatosis; esophageal constriction.

Case. Sex. Date. Age.	Symptoms.	Physical findings.	Roentgen-ray findings.	Clinicai diagnosis.	Remarks.
238,498 7/12/18 M. 45	Five months; loss of weight; cough; dyspnea; pain.	Immobility of right side of the chest; dullness extending to apex; increase in vocal resonance.	Retraction of right chest; increased density throughout right lung, particularly in lower two-thirds; increased density of right apex; emphysema of left chest; left apex clear.	Malignant disease of right lung and pleura.	Blood-tinged fluid obtained on repeated tappings of right chest.
288,632 9/10/19 M. 64	Three months; weight loss 30 pounds; slight cough; dyspnea; pain on swallowing.	Harsh breath sounds and increased fremitus in left lower lobe.	Small circumscribed shadow extending from left hilum; increased density of right hilum; few small areas in lungs uggestive of metastasis; apices clear.	Malignancy of lungs.	
330,230 8/20/20 F. 69	Thirty months; weight loss 25 pounds; severe cough; dyspnea; slight hemoptysis seven months ago.	Signs of consolidation in left lung.	Dense shadow filling left chest, except apex and base, which were translucent shadows indicative of metastasis in right lung.	Primary malignancy of lungs.	1/21 death; necropsy not performed. Report from home physician: "The course of the illness confirmed the diagnosis."

particularly focused on the tumor masses. Further, the roentgenogram is seldom made immediately before the death of the patient; owing to the usual lapse of time between the two events, the condition seen at necropsy is likely to be more extensive than that indicated by the Roentgen-ray examination, and may be radically altered. In the third place, a large dense shadow does not necessarily signify a solid tumor mass, but

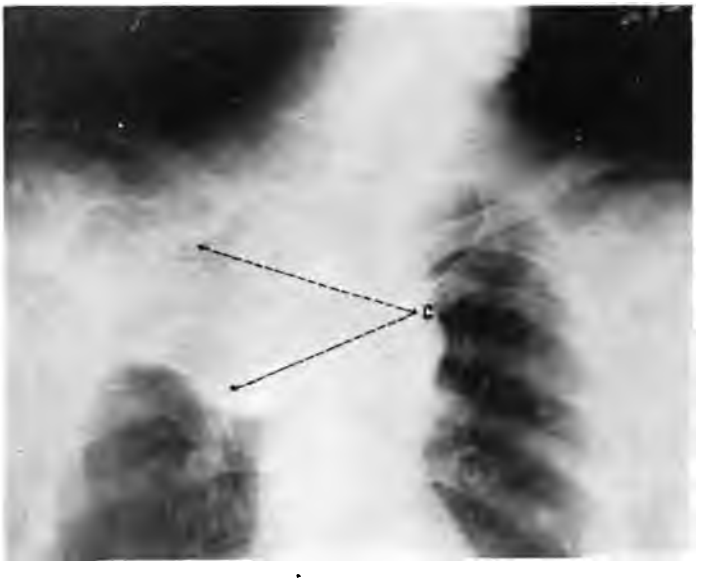

Fig. 61.—(Case 1921, 191.) Lobar type. Dense shadow in the right upper lobe. No shadows indicating metastases. Case proved by necropsy; specimen, Fig. 62.

may result from the overlapping shadows of a multitude of small tumors.

Any classification into roentgenologic types is more or less arbitrary, and the most simple one seems most desirable. Following Arnsperger, Jaugeas, Barjon, and Otten, therefore, we may recognize two main general types with respect to the situation of the principal shadows, namely, hilar and lobar, subdividing them as necessary. A convenient classification of the

37 cases here reported could be expressed diagrammatically as follows:

1. Lobar cancer, 14 cases.

A. Massive shadow involving part of a lobe, an entire lobe or more, accompanied or not accompanied by smaller shadows

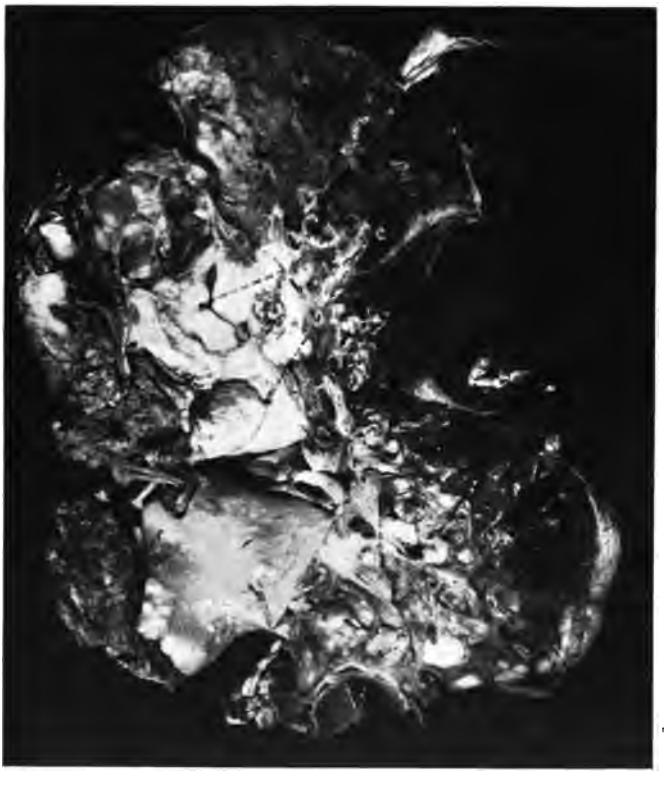

Fig. 62.—(Case 1921, 191.) Photograph of specimen. Lung laid open, showing carcinomatous tissue at *c* (Table I).

in the pulmonary field (metastatic areas). Of these there were 12 cases, in 6 of which the large shadow was solitary, the other 6 showing small metastatic shadows in variable number (Figs. 61–65).

B. Multiple small diffuse shadows in the lung fields, evidently

metastatic, but with no parent shadow distinguishable, the miliary form; 2 cases were of this variety (Fig. 66).

2. Hilar cancer, 23 cases.

A. Mass shadow at the root of the lung, with rounded, circumscribed, clear-cut border, 7 cases (Figs. 67–70).

Fig. 63.—(Case 1920, 363.) Lobar type. Entire left chest densely shadowed; thinning out somewhat above. Heart displaced to the left. Case proved by necropsy (Table I); specimen, Fig. 64.

B. Mass shadow at the root of the lung, with prong-like projections from its border, or rounded with a hazy margin, 16 cases (Figs. 71, 72).

The massive shadows of the lobar type (A) varied in general outline; some took the form of the lqbe which was completely involved, others were somewhat quadrilateral. In the main the shadows were markedly dense and fairly uniform except

at their periphery, where, unless they extended to the thoracic wall, they showed a hazy thinning out. In one case the shadow was mottled and of variable density throughout.

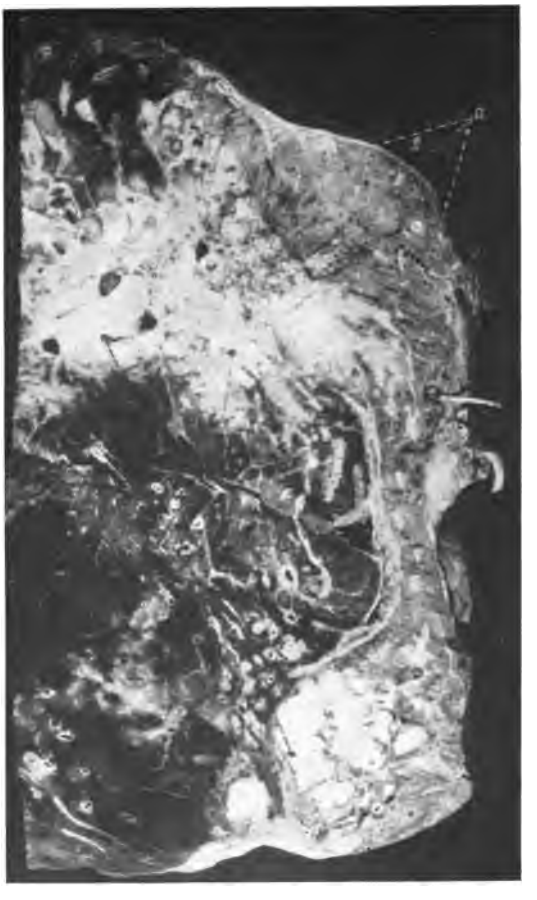

Fig. 64.—(Case 1920, 363.) Photograph of specimen. Left lung solid with areas of carcinoma (*c*) scattered throughout collapsed lung (*a*) (Table I).

The cases of the miliary variety (B) were exactly similar to miliary metastasis from an extrathoracic focus, and the roentgenogram did not show any particular shadow which could be assumed to be the original lesion. It would be absurd

to suppose that each miliary nodule represents a primary focus; rather is it to be assumed that the innumerable small nodules are metastatic from one undiscovered focus either at the root or elsewhere in the lung, no extrathoracic primary growth being found. Nevertheless, Adler's reserved attitude toward such cases is not unreasonable, since miliary metastatic nodules

Fig. 65.—(Case 160,751.) Lobar type. Massive shadow in the right middle lobe. Metastasis in both lungs. In our experience this type with metastases has been pathognomonic. Case proved by necropsy.

in the lungs from cancer of other organs are relatively common, and search for an outside focus should be thorough.

In the first subtype of hilar lesion (A) the margin of the growth was smooth and regular, and contrasted sharply with the lung field, while the second subtype (B) exhibited either spur-like protuberances from the border, or the margin was

hazily delineated. It may be assumed that in the first instance peripheral extension of the tumor was more or less sharply limited from the surrounding tissues, while in the second the growth had become irregularly infiltrating.

Fig. 66.—(Case 355,483.) Miliary type. The multiple shadows are of metastases; the primary lesion was believed to be in the lung, as none could be discovered elsewhere. The primary focus may have been small as in Case 1921, 239, in which there was metastasis to the spine. Biopsy: Cervical lymph-node carcinomatous.

The relative frequency of the various types and subtypes in this series is shown by the statistical figures. The marked preponderance of hilar over lobar lesions (23 to 14) is consistent with the more common origin of these cancers from a principal bronchus. It is noteworthy also that two-thirds of the hilar

lesions gave Roentgen-ray evidence of actively invading the pulmonary parenchyma.

Twenty-nine of the entire series of patients were men; 7 were women. The average age was fifty years; the youngest patient, confirmed by necropsy, was seventeen.

Fig. 67.—(Case 328,955.) Hilar type. Large dense circumscribed shadow projecting from the left hilum. On this side the lung is collapsed, producing pneumothorax, which is especially well seen above the shadow. In the right hilar region is a less dense, smaller, circumscribed shadow. Small amount of fluid in the right base. Apices clear. Case proved by necropsy.

Roentgenologically the predominating shadows were in the lung fields (lobar) in 14, 2 of these being of the miliary variety, and in the hilar region in 23. Of the lobar cases, the principal shadow was in an upper or middle lobe in 7, in a lower lobe in 5. Of the hilar cases, 6 showed sharply circumscribed lesions,

while 16 had irregular margins. Roentgen-ray evidence of fluid was noted in 6 cases.

In the cases proved by necropsy alone similar proportions were found with 6 lobar, 1 miliary, and 10 hilar lesions. Seven of the hilar lesions had irregular borders. Roentgenographic signs of fluid were seen in 2 cases.

Fig. 68.—(Case 270,910.) Hilar type. Large circumscribed hemispheric shadow projecting from the left hilum to the lateral chest wall. Clinically, primary cancer; death one year after examination.

The necropsy findings show certain divergences from those reported by the roentgenologist, due mainly to the continued progress of the disease after the Roentgen-ray examination. Thus fluid was found at necropsy in 10 cases, the amount ranging from a few cubic centimeters to 1600. Cavities were found in 3 cases; in 2 of these the cavities were small and filled with

pus; in 1 case there were three large cavities which had not been shown by the Roentgen ray. The bronchial origin of the tumor was established by the necropsy in 5 cases, the lobar origin in 2, and the origin was not determined in 10.

I have reviewed the cases of primary cancer of the lung largely for the purpose of determining, if possible, whether

Fig. 69.—(Case 1921, 8.) First examination. Dense circumscribed shadow extending from left hilum.

there are any characteristic Roentgen-ray signs of primary cancer of the lungs. One appearance, namely, a dense lobar shadow with smaller areas suggesting metastasis, I consider pathognomonic (Fig. 65). However, it should be apparent that because of the varying situation, the extent and general gross character of the lesions, and because of complicating factors, such as pleural effusion, interference with the pulmonary

circulation, atelectasis, bronchiectasis, tuberculosis, and other pneumonic processes, there can be no constant Roentgen-ray picture of cancer of the lung. But there are certain Roentgen-ray findings which should lead the roentgenologist to suspect its presence. Among these are:

1. A large dense shadow involving a portion of a lobe, an entire lobe, or more, with hazy margins throughout or only partly clear-cut, sparing the apices and associated with shadows

Fig. 70.—(Case 1921, 8.) Second examination. Shadow at left hilum increased in size. Veiling of left upper lobe.

at the root of the lung, or extending to it. Such findings, if associated with smaller shadows indicative of metastasis, I would consider pathognomonic of primary cancer.

2. A dense shadow at the root of the lung, variable in size, with a convex outer border, either smoothly curved or with linear shadows jutting from the border. Occasionally, the lung field peripheral to the tumor may show a slight increase in density due to passive congestion or atelectasis.

3. Miliary lesions in both lungs with or without a gross parent shadow.

In other words, in the classic and more common cases of primary cancer the principal Roentgen-ray shadows are characterized by marked density and irregularity of shape; are more likely to be situated at the root of the lung or in an upper lobe,

Fig. 71.—(Case 296,247.) Hilar type. Large dense shadow with radiating periphery jutting out from the right hilum. Left hilar shadow somewhat enlarged. Biopsy: Supraclavicular gland carcinomatous.

or involve both; are seen more often on the right side; affect one lung only or at least chiefly; and are often accompanied by smaller shadows of local metastasis, although generally less numerous than in metastasis from extrathoracic lesions. However, classic cases cannot routinely be expected, and the examiner should keep in mind the inevitable exceptions.

With present limits of knowledge and experience it is hardly conceivable that in the earliest stages of pulmonary cancer a well-founded diagnosis could be made by any method. For example, in one case of this series (Case 1921—369), in which death occurred from spinal metastasis, the roentgenograms

Fig. 72.—(Case 199,262.) Hilar type. Dense wedge-shaped shadow with irregular borders extending downward and outward from the right hilum. Density of left hilum exaggerated. Lung markings accentuated, especially on the left. Apices clear.

(Figs. 73, 74) gave no diagnostic evidence of the small bronchial cancer discovered at necropsy. However, patients seldom come for medical attention until the growth has attained substantial proportions, and at this stage the discovery of at least a pulmonary lesion is not usually difficult. By its demonstration of unwonted shadows the Roentgen ray particularly excels

in this field. Whether the revelation of an abnormal condition can be carried to a complete diagnosis depends on numerous circumstances; in some instances the Roentgen-ray examination alone may be reasonably decisive, in many a combination with the clinical findings will be necessary in order to form a conclusion, and in a small minority no positive decision can be made after the application of every test, for all methods, short

Fig. 73.—(Case 1921, 239.) Lung fields clear. Slight accentuation of each hilar shadow. No Roentgen-ray evidence of small bronchial cancer found at necropsy. Death due to metastasis to the spine; specimen, Fig. 74.

of a careful necropsy, may fail to make the diagnosis, as I have observed in more than one instance (Figs. 75–80).

The lesions from which primary cancer of the lung must be differentiated are quite numerous, and the ability to make such differentiation will depend on the examiners' familiarity with the Roentgen-ray signs of the different diseases. Among these lesions are:

Simple chronic pleuritis, pleural plaques, interlobar effusions, encysted empyemas, bronchiectasis, pneumonokoniosis, post-influenzal processes, abscesses, gangrene, cysts, lobar pneumonia, syphilis of the lung, mediastinal new growths, aneurysms, Hodgkin's disease, sarcomas, benign tumors, tuberculosis, and metastatic malignancy.

Simple chronic pleuritis and pleural plaques, as seen roentgenologically, commonly involve the surface of one lung. In

Fig. 74.—(Case 1921, 239.) Photograph of specimen. Carcinomatous tissue in left bronchus at *c*.

pleuritis the affected area shows as a veiling, somewhat irregular in density, through which the ribs can be seen. Plaques are likewise irregular as to density, variable in size and shape, are circumscribed in outline, and often contain calcareous material.

Pleural effusion, serous, sanguineous or purulent, commonly extending from the base upward, obliterating the costophrenic angle, most often unilateral, and showing a horizontal fluid

level above or the curved line of Damoiseau, is familiar in its Roentgen-ray aspects, and not likely to be confounded with cancer of the lung. Change of the fluid level with changing position of the patient is distinctive. Fluid accumulations occur in association with cancer, but usually other manifestations of the latter are also visible elsewhere in the thoracic field. Extensive collections may mask intrapulmonic evidences of the growth, and in suspected cases reray after paracentesis

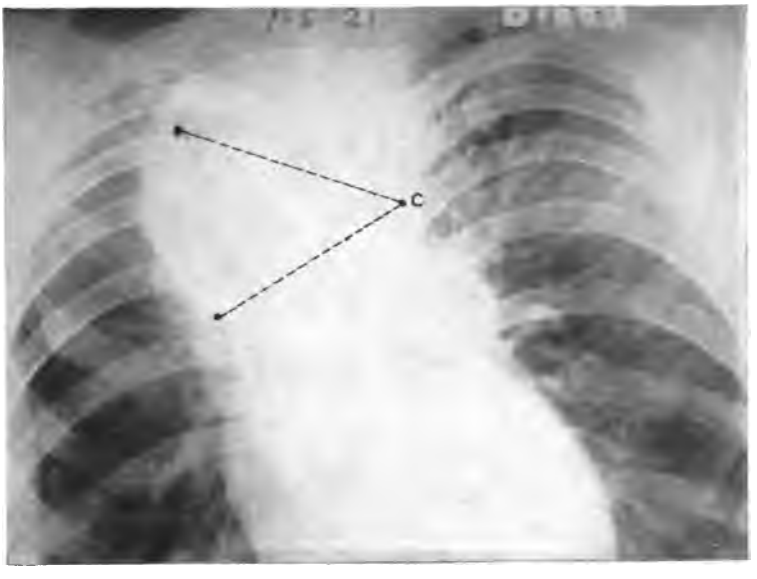

Fig. 75.—(Case 1921, 147.) January 5, 1921. Circumscribed shadow involving part of right upper lobe.

is advisable. Although in 12 per cent. of Adler's cases fluid was reported to be present, the amount was often small; on the whole, this condition should seldom be a serious obstacle to diagnosis.

Encysted empyema is likely to give a rounded or oval shadow of sharp outline, often mesially situated and seldom multiple. A gas bubble, sometimes quite small, may occasionally be seen in the top of the shadow.

Interlobar effusion, as I have seen it and as seen by Ass-

mann, gave a single rounded shadow of moderate, uniform density, well out in the lung field, with clear lung tissue around it, and was not connected with hilar shadows. Such a shadow with its obvious interlobar location and unaccompanied by shadows suggesting metastasis would be indicative of interlobar effusion rather than primary cancer.

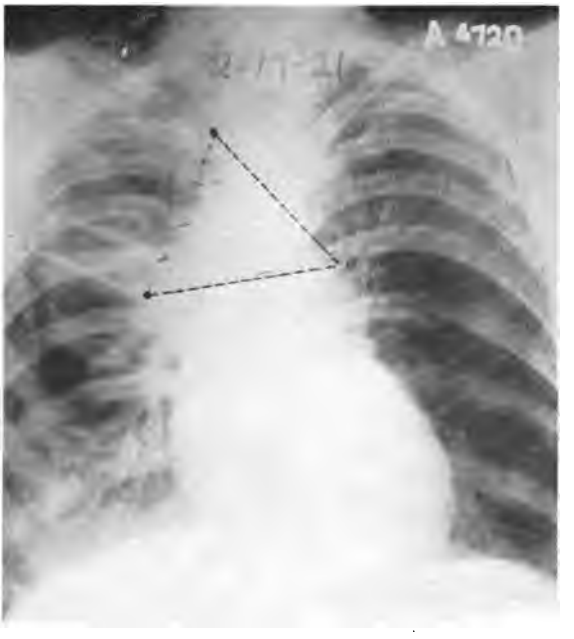

Fig. 76.—(Case 1921, 147.) February 17, 1921. Shadow in right upper lobe has largely disappeared, leaving heavy linear radiations.

Bronchiectasis has been described by Moore as of three types—infiltrative, cylindric, and sacculated. The first type has a roentgenologic resemblance to chronic bronchitis; the second produces a fan-shaped mottling with greatest density at the hilus and showing one or more small pseudocavitations; the third type shows larger multiple pseudocavitations, 1 to 3 cm. in diameter, surrounded by dense fibrous tissue. Only

the second or third types are likely to be confounded with cancer, but, as the lesions are often bilateral and somewhat symmetric, they would hardly be confusing.

In this connection it should be emphasized that primary cancer originates from one focus, and hence is always unilateral in its early stages at least. No one has ever reported a primary

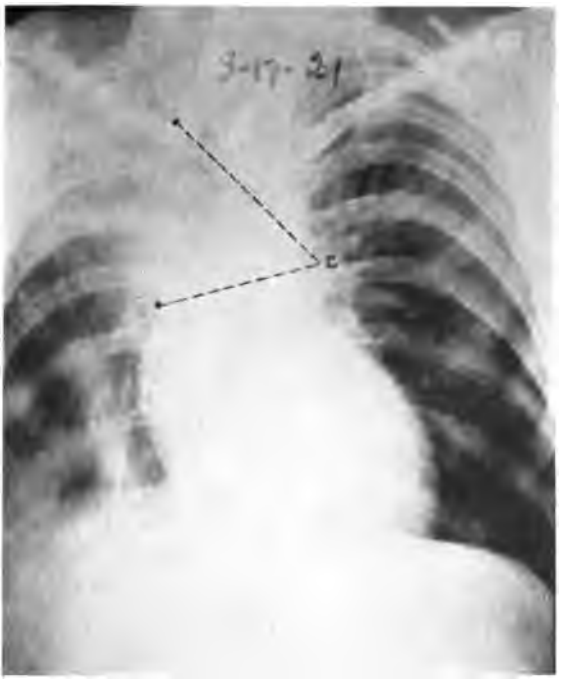

Fig. 77.—(Case 1921, 147.) March 17, 1921. Shadow similar to that seen at first examination (Fig. 75).

cancer of bilateral or multiple origin. Both lungs can be involved either by extension of the focal growth or by metastasis. For these reasons we may expect the Roentgen-ray evidences of the disease to be manifest only in one lung, or, if both lungs are invaded, to predominate on the side where the original lesion is located. Therefore, a bilateral and symmetric lesion is probably not primary cancer.

Pneumonokoniosis of the advanced type shows patchy shadows of variable density and size situated in the subapical region. It is bilateral and fairly symmetric. In the more chronic cases the dense shadows may suggest consolidation. In this lesion the roentgenologic characteristics are so different from primary cancer that the two diseases are not likely to be confounded.

Fig. 78.—(Case 1921, 147.) March 24, 1921. Shadow now involves right upper and middle lobes.

Abscess of the lung commonly appears as a single shadow of moderately increased density, variable in shape, sometimes round, with a hazy, irregular border. When partially evacuated the fluid level of the remaining contents makes the picture characteristic. Gangrene casts a shadow similar to that of abscess, but is less likely to show cavitation.

Hydatid cysts are usually single, though sometimes multiple; they tend to occur in the right lower lobe, and when unruptured produce a circumscribed rounded opacity. Primary cancer situated in a lobe seldom shows the roundness of cysts, but one of the cases reported by Cottin, Cramer, and Saloz gave a circular shadow in the right apex and was mistaken for a cyst.

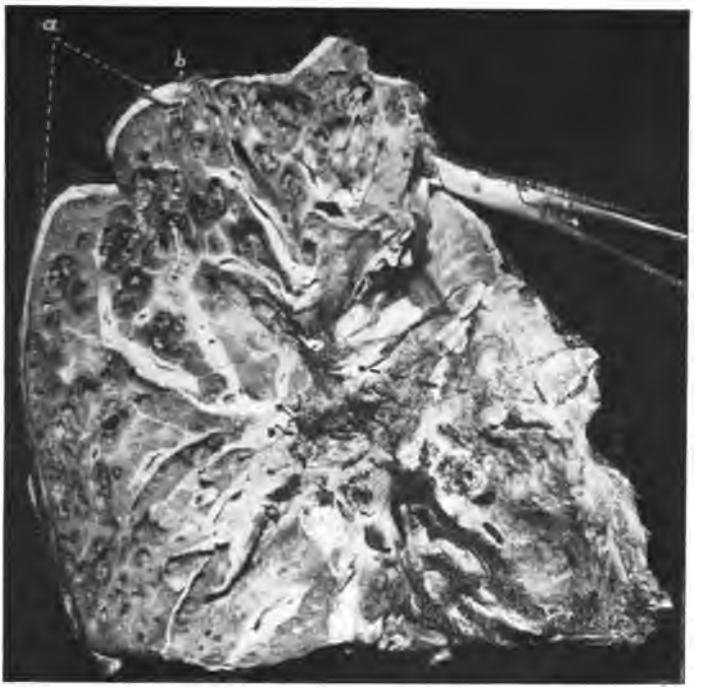

Fig. 79.—(Case 1921, 147.) Photograph of specimen: Thickened pleura (*a*); bronchiectatic cavities (*b*); carcinomatous tissue (*c*) (Table I).

Dermoid cysts are single, arise in the mediastinum, and are less opaque than hydatid cysts. Barjon comments on the perfect roundness of cysts, as though they had been traced by a compass.

The shadow of lobar pneumonia is less intense than that of carcinomatous infiltration. Commonly, the clinical history is quite definite. Even without such a history the rapid suc-

cession of changes observed roentgenologically would point to the diagnosis. Christie has seen slowly resolving bronchial adenopathies and localized pneumonic processes following influenza or caused by *Streptococcus hemolyticus*, which he thinks might be mistaken for malignancy of the lung.

Fig. 80.—(Case 109,685.) Specimen of miliary type of pulmonary cancer.

Syphilis of the lung, because of its infrequency, will not often enter into the differential diagnosis, although a few fairly well-proved cases have been reported. Assmann recounts a case in which a Roentgen-ray examination by Forssell showed enlargement of both hilus shadows, especially intense on the right, with a consolidation as large as a "goose egg" and branches

radiating into the pulmonary tissue. At necropsy this consolidation was found to be made up of connective tissue, strands of which extended into the upper and middle lobes. In one of our own cases the median shadow was markedly enlarged, with increased density along the main bronchi. In addition, the heart was enlarged and the aorta dilated. At necropsy patchy fibrous infiltration was found around each hilus, also

Fig. 81.—Hodgkin's disease, proved by biopsy.

a saccular aneurysm of the aorta. Rare instances of gumma in the pulmonary parenchyma have also been recorded. Christie illustrates a case with a large gumma near the right hilus, which shows considerable similarity to an early cancer of the lung. In most cases of syphilis of the lung, however, associated cardiovascular changes are to be expected, and the condition is thus likely to be surmised.

Aneurysm with its sharply delimited shadow extending from the mediastinum requires differentiation only from a smooth hilar cancer. Expansile pulsation, as noted on the screen, would make the differentiation. In the occasional absence of this pulsation a history of syphilis or a positive Wassermann reaction may be decisive.

Fig. 82.—Hodgkin's disease, proved by biopsy. This lesion might easily be mistaken for primary cancer of the lung.

Primary sarcoma of the lung is much more infrequent than carcinoma. So far as my knowledge goes there has been no proved case in the Mayo Clinic. In any event absolute differentiation of the two conditions would of necessity be microscopic.

Lymphosarcoma and Hodgkin's disease practically always originate in the mediastinum. In lymphosarcoma the tumor

is more often bilateral, of wide extent and rapid growth, and has a tendency to metastasize. Hodgkin's disease manifests itself in one of two ways:

1. A bilateral and fairly symmetric projection from the mediastinum, extending the entire length of the median shadow. Its borders may be undulated and either clear-cut or irregular.

Fig. 83.—Hodgkin's disease, proved by biopsy.

This picture is quite diagnostic and not to be confounded with carcinoma (Fig. 81).

2. A unilateral projection from either hilum with a circumscribed or ragged margin. This type cannot be distinguished roentgenologically from primary cancer (Figs. 82, 83).

Among the measures which may be required for a definite diagnosis is a biopsy of accessible lymph-nodes or after thoracotomy. Exceptionally, Hodgkin's disease may involve

the parenchyma of the lung; in one of our cases there were definite metastatic nodules in the lung field.

Benign tumors cannot be excluded with perfect assurance, but they are rare, remain stationary for long periods or progress slowly, and are likely to have well-defined margins. Jacobaeus and Key have reported 6 cases of pulmonary tumor, all of which were benign save one, a fibroxanthosarcoma. All the roentgenograms show a single, rounded, dense, clear-cut shadow. Four of the shadows projected from the mediastinum; two were in the left upper lobe. These writers dwell upon the diagnostic value of thoracoscopy and Roentgen-ray examinations before and after the induction of pneumothorax.

Tuberculosis with extensive areas of caseous pneumonia may imitate primary cancer. Apical involvement, absence of extensive hilus shadows, and cavities speak for the former. The cavities found at necropsy in many of our cases of primary cancer were filled with necrotic débris and were not visible on Roentgen-ray examination. I have not noted their observation in the case reports or illustrations of other roentgenologists. Steyrer states that such cavities are rarely demonstrable roentgenologically because they are small and surrounded by dense tissue. On the other hand, it is to be borne in mind that tuberculosis and cancer of the lung may exceptionally coexist. Chronic tuberculosis of the miliary type gives smaller individual areas of density with greater uniformity of size than the secondary miliary nodules sometimes incident to primary cancer of the lung. No association of tuberculosis with carcinoma was observed in any of our cases that went to necropsy.

Metastatic cancer of the lung occurs in two principal forms, the gross nodular and the miliary. Gross metastatic nodules are commonly multiple, of various sizes, round, bilaterally distributed, and sharply circumscribed. Miliary metastasis from extrathoracic foci is usually bilateral, symmetric, and unaccompanied by any large dense area in the lung which might be regarded as the primary source. Obviously, however, the original focus could be in the lung and so small as to escape detection. Absolute distinction between primary

and metastatic cancer, when no extrathoracic focus can be demonstrated, can be obtained only by exhaustive examination at necropsy.

SUMMARY

Primary cancer of the lung is not a common disease, yet it occurs often enough to make its diagnosis important. Its symptoms are by no means pathognomonic. The condition often fails of clinical recognition, and it is frequently mistaken for tuberculosis. The Roentgen-ray examination is of valuable assistance in diagnosis.

Pathologists have found that the most common origin of the growth is in a large bronchus (either from bronchial epithelium or from the bronchial mucous glands), but it may arise from alveolar epithelium. Two principal types are found at necropsy, one producing a mass surrounding a bronchus, the other invading large portions of the lung. In addition to the primary tumor masses pathologic complications often occur, such as metastasis, atelectasis, circulatory stasis, pneumonic processes, and pleural effusions. Corresponding to the pathology, two chief roentgenologic types may be recognized, one in which the shadows are largely lobar and one in which they are principally hilar. The lobar shadow is often extensive and may or may not be accompanied by some smaller shadows of metastasis. A less common lobar type, the miliary, may appear as multiple small shadows in both lungs. Two varieties of the hilar type have been observed, one rounded and circumscribed, the other with an irregular border and shadowed extensions.

The extensive, dense, lobar shadow attended by smaller shadows of metastasis I consider to be pathognomonic. All other varieties require careful interpretation in the light of the clinical facts.

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CARDIOSPASM: A REPORT OF 301 CASES

HENRY S. PLUMMER AND PORTER P. VINSON

SINCE 1878, when Zenker and von Ziemssen reported the first series of cases of cardiospasm, much has been written concerning this interesting condition. Various authors have reported a fairly large number of cases, but the final results of treatment have rarely been summarized. Although the various hypotheses concerning the etiology of the disease are rather interesting, it is beyond the scope of this paper to duscuss them. None of them satisfactorily explains all the cases that come under observation.

The hypothesis that the spasm at the cardia is reflex in origin and dependent on some gross intra-abdominal lesion may seem justifiable in a limited number of cases, but a study of a larger series makes it untenable. A few of the cases observed in the Mayo Clinic have been associated with duodenal ulcers, but whether or not the spasm was due to the ulcer is open to question. Fissure at the cardia or local disease in the esophagus may be present, but is not a constant finding.

Cardiospasm, although not a common affection, is more deserving of mention than is usually accorded it in text-books, and consequently the general practitioner is apt not to be familiar with its manifestations. It is, however, a condition worthy of serious consideration because of the distressing symptoms and the ease with which it can be relieved.

Cases of cardiospasm may be divided into two main groups. In the first group are cases in which there are mild symptoms of spasm, such as pain on swallowing, a feeling of food obstruction, and regurgitation, but without dilatation of the esophagus, and demonstrable obstruction at the cardia. Patients of this group are frequently psychoneurotic types. Unquestionably

many of them develop more pronounced symptoms as the disease progresses. Many require forcible dilatation of the cardia to relieve their symptoms, but some are cured by the use of antispasmodic drugs. Spontaneous cure is sometimes seen. In the second group are the cases in which the symptoms may be quite as mild as in the first group, but are usually much more severe. Patients of this group have a demonstrable obstruction at the cardia with varying degrees of esophageal dilatation. As a rule they are not psychoneurotic.

The series of cases described here belongs to the second group, since it does not seem justifiable to draw definite conclusions from a study of the patients in the first group. We have not included in this study a group of 40 cases previously reported by one of us (Plummer). Sufficient data could not be obtained to make them of very great value.

The age of the patients at the time of examination varied from five to eighty-three years (Table I); 137 were females and 164 were males. The duration of symptoms varied from two months to forty years (since these cases were collected a patient aged fifty-five years has come under observation who had had symptoms for forty-five years). The average duration of symptoms was seven and forty-nine hundredths years. The onset of symptoms was sudden in 45 cases and gradual or not stated in the others.

TABLE I.—AGE

Decade.	Patients.
1 to 10	4
11 to 20	21
21 to 30	68
31 to 40	86
41 to 50	67
51 to 60	33
61 to 70	17
71 to 80	3
Over 80 (83)	1
Age not given	1

SYMPTOMS

As pointed out by Plummer, the symptoms vary somewhat according to the stage of the disease. No attempt was made

to separate the cases into the three stages previously described; this may be done, however, by careful analysis in many instances.

1. **Dysphagia.**—All of the patients had varying degrees of dysphagia. Some of them noticed only a slight hesitation of the bolus of food at the cardia; one patient had not been able to get food past the cardia for eighteen years, all nourishment having been obtained through a gastrostomy tube; 53 patients had had complete closure, and neither solids nor liquids passed into the stomach for twenty-four hours or more. Because of this difficulty in swallowing marked nutritional disturbances were common; 201 patients had lost weight, 1 patient having lost 90 pounds in three months.

The type of food producing dysphagia was not constant; the majority of patients complained of having as much difficulty with liquids as with solids. Cold drinks, pop-corn, and apples seemed to cause the greatest difficulty.

2. **Regurgitation** often occurred immediately following the ingestion of food or was delayed for hours, depending on the amount of food taken, the dilatation of the esophagus, and the tonicity of the esophageal walls. Nocturnal regurgitation, awakening the patient from sleep by food or mucus running out of the mouth or into the nose, producing cough, or staining of the pillow by food particles or mucus, without associated discomfort, occurred in 89 cases. The regurgitated material was always described as consisting of ropy mucus or food unchanged by digestion. Eleven patients stated that blood had been mixed with the regurgitated material; 9 noticed only small streaks, while 2 noticed a considerable amount. The material regurgitated did not contain free hydrochloric acid. Test-meals were given to 78 patients and free acid was absent in 52. This was due to the fact that esophageal and not gastric content was recovered; the stomach-tube had failed to pass the cardia. Regurgitation usually occurred without the effort or retching that occurs with ordinary vomiting.

3. **Pain.**—One hundred and forty-two patients had pain in the epigastrium radiating substernally and at times to the back. In 52 pain was the initial symptom. One patient had attacks

of epigastric pain for fourteen years before dysphagia began; 77 considered pain to be the chief feature of their disease.

The pain varied in intensity from mild discomfort to severe attacks requiring hypodermic injections of morphin. The severe attacks at times resembled gall-stone colic, and at times differentiation was difficult. Although the pain was usually associated with deglutition, it came on frequently independent of the time of food ingestion. Following forcible dilatation of the cardia attacks of pain were often noted, coming on as late as thirty-six hours afterward. Patients who had not previously had pain were quite as likely to develop such attacks as those who had had pain as part of their symptoms.

One patient who for months, at intervals of one week or ten days, had had attacks of pain which required $\frac{3}{8}$ gr. of morphin for relief was esophagoscoped without anesthesia. A sound was passed through the cardia and immediately a colic was induced, and the cardia was seen to contract spasmodically. A hypodermic injection of morphin relieved the pain. This was repeated at a second examination. Stretching of the cardia relieved all the symptoms.

4. **Respiratory Symptoms.**—Pulmonary symptoms were noted in 25 patients, most of whom had a cough at night due to regurgitation. Several of the patients had dyspnea after eating from the pressure of a large dilated esophagus filled with food. One patient had attacks simulating asthma that came on after meals and were relieved by regurgitation. Only 3 of our patients had pulmonary tuberculosis. This seems quite remarkable when one considers the general poor nutrition seen in so many of these patients.

ASSOCIATED CONDITIONS

Syphilis was a complication in 6 cases. A blood Wassermann test was made in 55 cases, with two positive results.

Psychoneurosis.—Contrary to the general belief, cardiospasm is not a psychoneurosis, and patients suffering from it are usually calm and well-balanced, with normal nervous systems. Forty-one patients had associated neurotic complaints.

DIAGNOSIS

The diagnosis of cardiospasm in most cases is relatively simple, but at times very careful study is necessary. Given a patient of any age who has had dysphagia extending over a period of from five to six years, without increasing symptoms, who is having as much difficulty with liquids as with solids, with no history of previous trauma to the esophagus, and in whom roentgenograms reveal a smooth cigar-tip type of obstruction at the cardia, with or without dilatation of the esophagus, the diagnosis of cardiospasm is probable. If in addition to this a No. 45 French olive can be passed into the stomach guided by a previously swallowed silk thread with no more than slight resistance at the cardia, the diagnosis is practically certain. If there is no obstruction to the passage of a No. 45 French olive, retention of the opaque meal with dilatation of the esophagus is rarely if ever seen in any condition other than cardiospasm. An esophagoscopic examination in the majority of cases is quite unnecessary, and such examination is usually more difficult than the examination of other ordinary obstructions because of the large retention of mucus in the esophagus. It is difficult to rid the esophagus of this mucus, and the knowledge obtained from the examination is usually not worth the effort.

Care should be taken not to make a diagnosis of cardiospasm on the evidence presented in a roentgenogram without having considered all features of the case.

Differential Diagnosis.—Cardiospasm must be distinguished from all lesions causing symptoms of esophageal obstruction, but carcinoma located at the cardia is the only lesion with which it may readily be confused. It is in such cases, in which the roentgenographic findings are accepted as diagnostic, that the majority of errors arise. The diagnosis of a pulsion diverticulum of the lower esophagus is sometimes made by the roentgenograms, but the condition is usually found to be cardiospasm with irregularity in the dilatation of the esophagus above the spasm; it is relieved by dilatation of the cardia. Three cases of true diverticulum of the lower esophagus have come under

our observation, and these, of course, present some difficulty in diagnosis. Whenever there is any doubt with regard to the correct diagnosis it is best to wait for several weeks or months before instituting treatment.

TREATMENT

Various forms of treatment have been employed in the management of cases of cardiospasm, including drugs, diets,

Fig. 84.—(Case 298,437.) Typical cardiospasm with moderate dilatation of the esophagus.

operations, and the passage of stomach-tubes and bougies. Fifty-eight of the patients in the series had been treated with medicines, stomach-tubes, and the passage of bougies; 17 had had operations for the relief of their symptoms, and 19 had had other operations during the course of their symptoms, but it was not definitely stated in their histories that the operations were performed because of the difficulty in swallowing.

Fig. 85.—(Case 307,429.) Cardiospasm with slight dilatation of the esophagus.

Fig. 86.—(Case 304,841.) Cardiospasm with marked dilatation and angulation of the esophagus.

Fig. 87.—(Case 351,320.) Cardiospasm with slight dilatation of the esophagus and an apparent filling defect at the cardia.

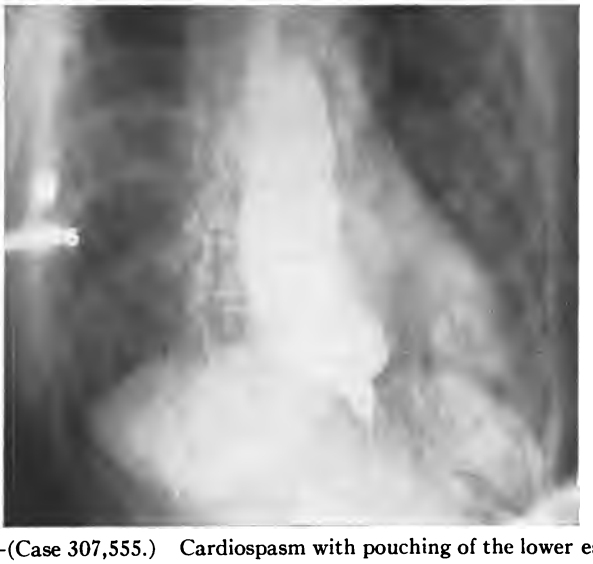

Fig. 88.—(Case 307,555.) Cardiospasm with pouching of the lower esophagus resembling a diverticulum.

The only treatment that gives satisfactory results is the forcible dilatation of the cardia. This was first done by opening the stomach and dilating the cardia manually. Our method of stretching the cardia is by means of a hydrostatic dilator designed and described by Plummer some years ago. One difficulty commonly encountered in dilating the cardia which has not been

Fig. 89.—(Case 292,948.) Carcinoma of the lower esophagus with moderate dilatation.

emphasized is the slipping of the dilator into the stomach or back into the esophagus when it is distended with water. The sensation of the dilator being pulled into the stomach or pushed back into the esophagus can be readily detected after some experience with such cases, and the difficulty can be easily over-

come by passing the dilator into the stomach, distending it, and pulling it forcibly up against the cardia. The water pressure is relaxed and the proximal end of the dilator is allowed to slip back into the esophagus. The water pressure is then rapidly renewed and the cardia is easily dilated. Air pressure may be used in place of water, but as air is more compressible than water, it is doubtful if the stretching is quite as effectual.

Fig. 90.—(Case 290,344.) Cardiospasm with the same contour and dilatation of the esophagus shown in Fig. 89, but without the filling defect.

Rupture of the dilator distended with water might be attended with greater risk than the dilator distended with air, but if ordinary care is used neither should cause trouble.

The pressure employed in stretching the cardia varies with the amount of dilatation of the esophagus above the spasm. When the esophagus is only slightly dilated the distention should not be more than from 20 to 25 feet of water pressure, whereas with the larger dilatations pressure to 30 feet is per-

fectly safe. Pain is usually induced when the cardia is dilated, but in some cases it is entirely absent, and the amount of pain bears no relation to the degree of pressure employed.

Ordinarily very little trouble is experienced in passing the dilator through the cardia where it is guided by a previously

Fig. 91.—(Case 350,031.) Carcinoma at the cardia, with a history of dysphagia of two years' duration. The roentgenogram is suggestive of cardiospasm.

swallowed silk thread, but in some cases it requires considerable manipulation. The reason for this difficulty is not always apparent. In one case recently reported it was due to marked angulation of the esophagus. We have not observed a case in which the dilator could not be passed through the cardia.

Results of Treatment.—The results of treatment in cases

of cardiospasm are most gratifying, and we believe that practically all patients can be cured if they are systematically followed up and the dilatations repeated if there is a tendency toward recurrence. The immediate results are almost spectacular. One dilatation, provided the cardia has been properly stretched, is sufficient to cure the majority of patients. Further dilatations are necessary in approximately 40 per cent. of the cases.

Fig. 92.—(Case 230,918.) Patient died from carcinoma of the stomach eight months after treatment for cardiospasm.

Almost all recurrences in this series of patients occurred during the first six months following treatment, and as the last patient of the series was treated nine months ago it is believed that the results herewith reported are true end-results.

It has been our experience that the longer the duration of symptoms and the larger the dilatation of the esophagus, the

Fig. 93.—(Case 318,719.) The patient had symptoms typical of cardiospasm previous to a plastic operation on the cardia twelve years before examination at the Clinic when cicatricial stricture at the cardia and marked dilatation of the esophagus were found.

greater the ease with which the patients are cured. The final results of treatment are shown in Tables II and III:

TABLE II.—THREE HUNDRED AND ONE PATIENTS WITH CARDIOSPASM

Hospital deaths	2 (0.66 per cent.)
Patients studied	299
Patients traced	246 (80.9 per cent.)
Deaths after dismissal	15 (6.9 per cent.)
Patients living	231 (93.9 per cent.)
One patient not dilated, only slight difficulty occasionally.	
One patient not dilated, no better.	
Patients dilated and completely relieved	187 (76.01 per cent.)
Slight difficulty (better than before dilatation)	42 (17.28 per cent.)
No better	15 (6.17 per cent.)

TABLE III.—FIFTEEN PATIENTS WHO DIED

Case.	Length of life after dilatation.	Cause of death.	Remarks.
230,918	8 months	Cancer of the stomach	Complete relief from cardiospasm
222,962	8 months	Influenza	Complete relief from cardiospasm
212,816	7 months	Tuberculosis	No relief from cardiospasm
42,154	1 year	Unknown	Slight difficulty at times
186,362	1 year, 3 months	Arteriosclerosis	Complete relief from cardiospasm
106,626	1 year, 9 months	Unknown	Complete relief from cardiospasm
208,520	2 years, 6 months	Cancer of the pancreas	No relief from cardiospasm
28,006	3 years	Stomach trouble	Some difficulty
97,322	4 years	Unknown	Complete relief from cardiospasm
22,547	5 years	Unknown	Complete relief from cardiospasm
52,983	6 years	Unknown	Complete relief from cardiospasm
10,045	10 years	Tuberculosis of the spine	Complete relief from cardiospasm
30,980	10 years, 3 months	Kidney trouble, influenza, and bad heart	No relief from cardiospasm
7,489	11 years, 3 months	Heart failure	Complete relief from cardiospasm
42,335	Not stated	Unknown	No report

The two deaths caused by rupture due to overdistention occurred among the early cases and were due to lack of knowledge with regard to the amount of pressure the cardia was able to stand. One of our patients, a woman, died from carcinoma of the stomach eight months after dilatation, and the diagnosis in this case might be questioned. Symptoms had been present for from five to six years and a roentgenographic examination showed a widely dilated esophagus above the point of obstruction. Dilatation was performed without incident and she was completely relieved from dysphagia. A letter received two months before her death stated that she had no difficulty in swallowing, but that she had distress in the upper abdomen after food reached the stomach.

CONCLUSIONS

1. Cardiospasm in the majority of cases is a definite entity and is not secondary to other lesions.

2. The disease is not a psychoneurotic manifestation.

3. Medical treatment is of no permanent value, and the passage of ordinary sounds does not stretch the cardia sufficiently to overcome the spasm.

4. Approximately 75 per cent. of the cases in the Clinic were cured by forcible dilatation of the cardia, and undoubtedly the majority of the remaining patients could be cured if dilatations were repeated. The dilatation can best be performed by a hydrostatic dilator.

5. The chief symptoms of the disease are dysphagia, regurgitation, pain, and pulmonary symptoms, such as cough and dyspnea.

6. Although roentgenographic examinations are of definite value, one should not attempt to base a diagnosis on these findings alone.

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ATYPICAL PAIN WITH ANGINA PECTORIS[1]

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THE sudden onset of retrosternal or precordial pain, radiating into the left arm or both arms, associated with the fear of impending death, with pallor, cold perspiration, etc., in a middle-aged person permits an unquestioned diagnosis of angina pectoris. Not infrequently, however, patients do not have typical symptoms, and it is this group I shall discuss.

Pain Mechanism in Angina Pectoris.—A knowledge of the mechanism by which pain and other reflex phenomena are produced in visceral disease is necessary for the comprehension of the typical and the atypical manifestations of angina pectoris. The nerve supply of the body is found in two great systems, the autonomic and the cerebrospinal. The former comprises the sympathetic nerves and certain cerebral nerves, of which the vagus only concerns us here. The organs and tissues which are supplied by the autonomic system are not endowed with sensation in the sense in which the term is applied to structures supplied by the cerebrospinal nerves.

It is well known that viscera, such as the heart, stomach, and bowels, can be handled and cut without producing pain. Violent contractions of unstriated muscular fibers, such as peristalsis of the exposed bowel, contractions of the uterus, etc., are, however, capable of producing pain, but the pain is felt in a different region from that in which the muscle lies. This regional discrepancy has an embryologic basis. In the primitive vertebrates, preceding the development of the limbs, each spinal nerve is distributed segmentally around the corresponding half of the body. In the higher scale of animal life as the limbs bud out from the trunk they drag with them away from the trunk portions of the nerve trunks, so that the regional

[1] Presented before the Southern Minnesota Medical Association, Winona, June, 1921.

nerve distribution becomes altered and often remote from the primary cord segmentation.

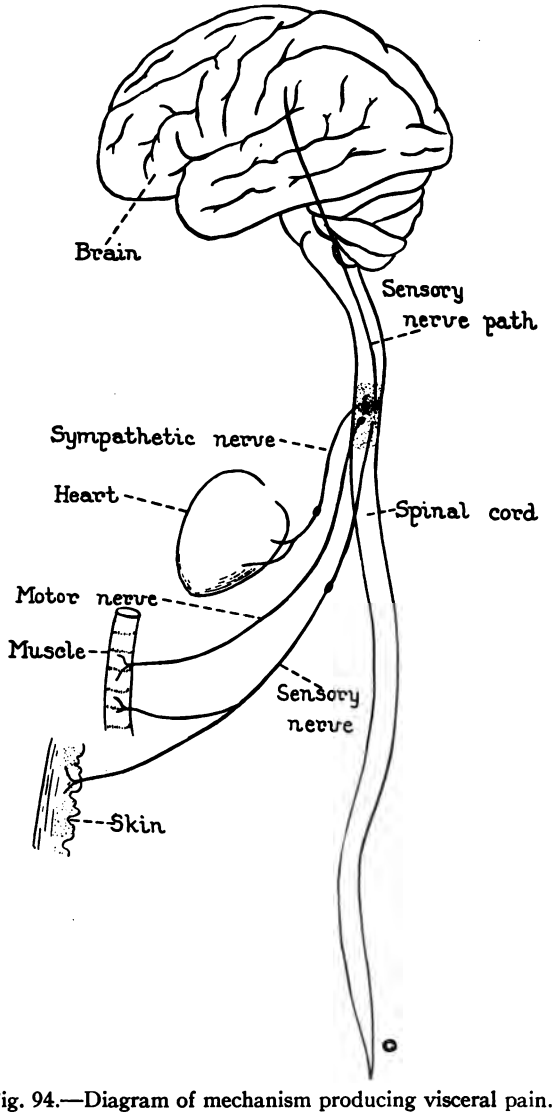


Fig. 94.—Diagram of mechanism producing visceral pain.

Stimulation of a nerve which ends in a sense organ, in any portion of its course from the periphery to the brain, conveys

a stimulus to the brain similar to that resulting when the sense organ is excited. Therefore, if a sensory nerve is stimulated in any part of its course from the brain to its ultimate distribution, the resulting sensation is referred to the peripheral distribution of the nerve in the external body wall.

Figure 94 diagrammatically represents the mechanism producing visceral pain. An abnormal stimulus arises in the heart and is conveyed to the spinal cord by the sympathetic nerve. On reaching the cord the stimulus is diffused beyond the sympathetic center and affects nerve-cells in the immediate vicinity. The cells thus excited respond according to their function. The sensory nerve causes a sensation which the brain interprets as pain and refers to the peripheral distribution of the sensory nerve in the skin. The motor nerve causes contraction of the muscle. This abnormal stimulation may leave a portion of the cord more irritable; it is represented in the diagram by the shaded area.

With these facts in mind it is readily seen how the abnormal stimuli of angina pectoris, varying in intensity and acting on thresholds of differing nervous irritability, may traverse unusual and remote nerve paths, resulting in a protean pain distribution.

Figures 95 and 96 represent the areas of distribution of the cutaneous nerves and their relation to the cord segments.

Mackenzie refers to the pain in visceral disease (viscerosensory reflex) as a protective mechanism, the alarm which awakens consciousness to the realization of trouble.

Character of Pain in Angina Pectoris.—Patients use numerous adjectives in describing their pain. It is frequently described as being oppressive in character, due probably to the association of dyspnea and apnea. Often the pain is said to be boring, aching, tearing, or sharp. On careful questioning, the patient frequently acknowledges a sense of chest constriction accompanying the pain, which is the result of the visceromotor reflex. A very important point in eliciting histories from patients is clearly to separate the areas of pain origin and pain radiation. Not infrequently the intensity of the pain radiated is greater

than that at the point of origin, and therefore the patient may describe only the sensations referred to the peripheral nerve

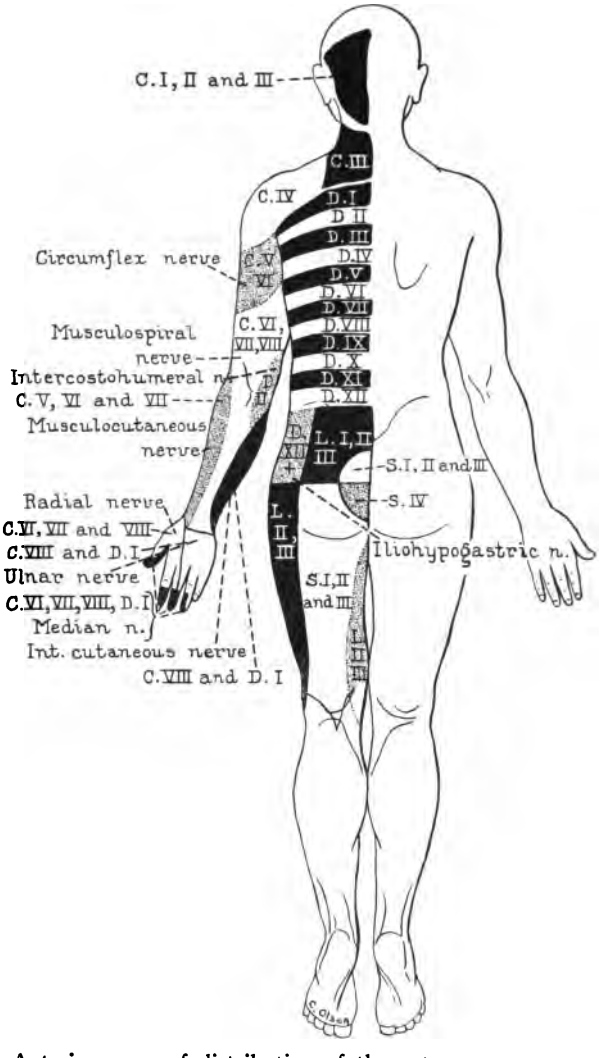


Fig. 95.—Anterior areas of distribution of the cutaneous nerves and their relation to the cord segments.

distributions. This at once calls attention to a possibility which may result in a misleading history.

Another very important point in history taking is to determine the factor or factors inducing pain. In the majority of

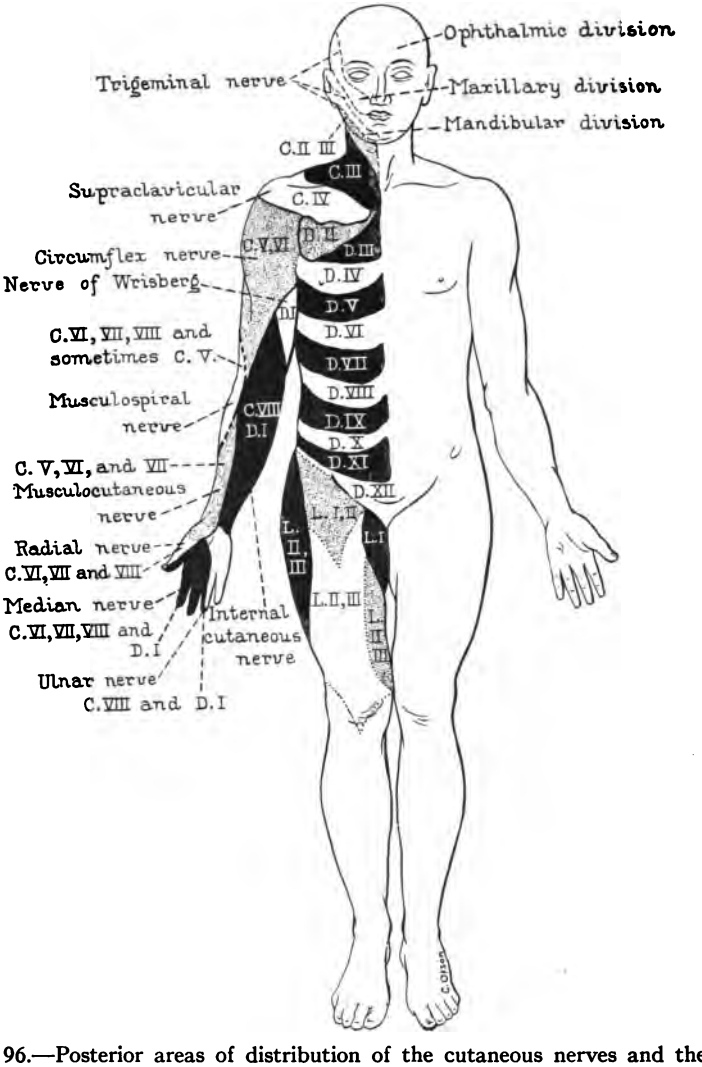


Fig. 96.—Posterior areas of distribution of the cutaneous nerves and their relation to the cord segments.

instances an anginal seizure is precipitated by exertion, emotionalism, such as anger and fear, or by eating. In my experience

the psychic status referred to as the fear of impending death, so greatly emphasized in the older publications, is far from being always present.

Nerve Paths Involved in Typical Angina Pectoris.—The usual pain radiation in typical angina pectoris is into the left brachial plexus, and it usually follows the distribution of the internal cutaneous and the ulnar nerves. Occasionally the pain follows the same nerve paths on the right side, and at times the radiation is symmetric. There are instances in which either or both arms are diffusely involved, when the nerves affected, besides the foregoing, are the circumflex, musculospiral, intercostohumeral, nerve of Wrisberg, the musculocutaneous, radial, and median.

Nerve Paths Involved in Atypical Angina Pectoris.—Neusser, in a very interesting manner, discusses pain aberration in angina pectoris. Involvement of the dorsal spinal segments by the abnormal stimuli of angina pectoris may cause pain in the back. The areas involved may be quite localized and often bizarre, at times limited to a relatively small area between the scapulæ. The stimuli may follow the distribution of the lumbar nerves, causing pain in the lower extremities, in the hypogastrium, and the testicle. Pain may be referred to the anus through the pudic nerve of the sacral plexus. Pain distribution through the dorsal nerves may be referred along the intercostal nerves, resulting in abdominal pain. The stimuli may radiate upward and follow the distribution of the trigeminus, giving rise to symptoms of toothache or facial neuralgia.

Neusser, in discussing the abdominal form of angina, designates the vagus and abdominal sympathetic paths as the course of the abnormal stimuli. This conception implies, I believe, the presence of disease involving the abdominal aorta, the involvement invariably being in the region of the celiac axis. Abdominal symptoms of angina, however, do occur when the abdominal aorta is not involved, occurring as the manifestation of true angina pectoris. As I have stated, dorsal segment distribution of stimuli may result in abdominal pain, which in character may simulate one of many abdominal conditions,

namely, gall-bladder disease, renal or ureteral colic, acute perforation of gastric or duodenal ulcer, etc. In this connection it is interesting to note that the pain accompanying acute visceral perforation, which usually is excruciatingly severe and persistent and accompanied by shock and collapse, may be exactly duplicated by coronary embolism.

The associated symptoms of angina pectoris, inconstantly present, are also dependent on nerve distribution. At times during the seizures esophageal symptoms are present, especially dysphagia and nausea, which result from vagus influences. Likewise, laryngeal manifestations, hoarseness, or aphonia may be present. Again, disturbances of the sympathetic innervation may occur, manifested by vasomotor changes resulting in perspiration, cold, clammy extremities, and also dilatation of the pupils.

REPORT OF CASES

Case I (244,920). Mr. L., aged forty-four, presented himself for examination complaining of severe cramping pain, limited to both pectoral regions, without radiation. Symptoms began four months before. The pain always occurred during exertion and subsided promptly with absolute immobility (Fig. 97). Examination revealed the heart to be normal in size (1.5 by 9.5 cm.), there was no arhythmia and no murmur. There was moderate sclerosis of the peripheral arteries. The systolic blood-pressure was 140, the diastolic 98. The electrocardiogram showed a rate of 71, with sinus rhythm. A diagnosis of angina pectoris with coronary sclerosis was made.

The pain in this case was unusual in its localized symmetry and lack of radiation. The second, third, and fourth dorsal segments were involved in this regional distribution (see Fig. 95).

Case II (211,811). Mrs. S., aged forty-two, complained of boring pain of two years' duration, arising in the lower right chest with radiation into the right arm, limited to the inner portion and involving the little and ring-fingers. The pain was induced by effort and of late had occurred daily (Fig. 98).

The heart was not enlarged (3 by 9 cm.). No arhythmia and no murmurs were present; the systolic blood-pressure was

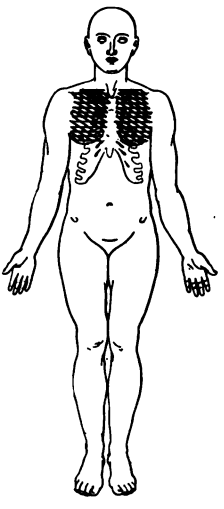


Fig. 97.

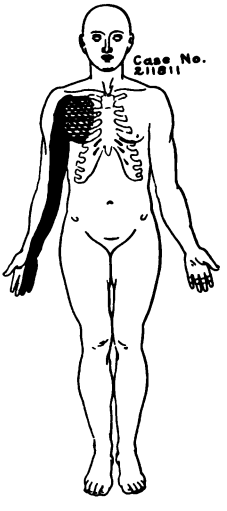


Fig. 98.

Fig. 99.

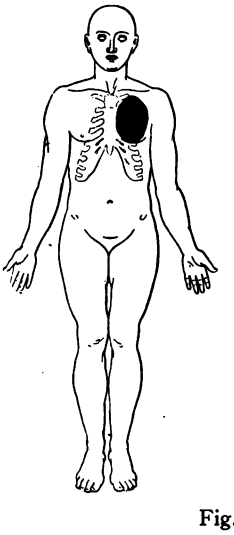
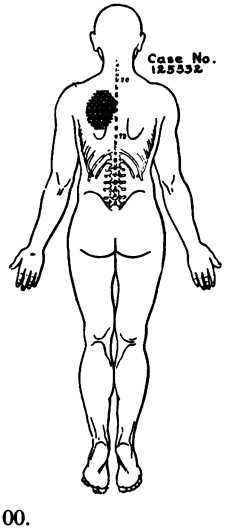


Fig. 100.



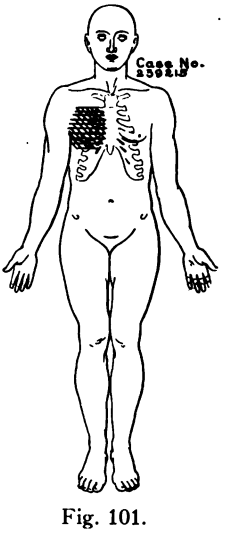


Fig. 101.

Figs. 97–101.—The shaded areas in the figures represent the region of the origin of pain, and the solid black areas the distribution of pain.

142, the diastolic 100; the electrocardiogram showed a rate of 72, with sinus rhythm, notching of the initial ventricular complex, Q R S in Derivation III, negativity of the final ventricular

T wave in Derivation III, and preponderance of the left ventricle.

The diagnosis was angina pectoris, with coronary sclerosis.

The isolated dextral distribution and limited arm radiation in this case were unusual. The right cord segments involved were the eighth cervical and first and second dorsal through the intercostohumeral, internal cutaneous, and ulnar nerves (see Figs. 95, 96).

Case III (198,206). Mr. C., aged fifty-two, gave a history of boring pain limited to the interscapular region, of three years' duration. The pain was brought on by exertion and usually lasted about half an hour (Fig. 99). The patient admitted having had syphilis. Examination revealed the heart to be greatly enlarged (6 by 18.5 cm.). The cardiac rhythm was occasionally interrupted by premature contractions. The rate was extremely slow. The pulsations discernible in the jugular bulbs were more rapid than the apical or radial pulse. This observation at once indicated dissociation of auricles and ventricles, which subsequently was confirmed by electrocardiography.

Loud to-and-fro murmurs were heard over the whole precordium, both murmurs were heard best over the aortic area. The systolic murmur had a deep, reverberant quality, while the diastolic was harsh and blowing. Capillary and water-hammer pulse and femoral pistol shots were present. The systolic blood-pressure was 170, the diastolic 44; the Wassermann reaction was negative; the electrocardiogram showed a rate of ventricles 47, auricles 94, and complete heart-block with occasional premature contractions of ventricular origin, preponderance of the left ventricle, and negativity of the T wave in Derivation I. T wave negativity in Derivation I alone is of great prognostic significance, associated with a cardiac mortality of 66.6 per cent. over a period of four and a half years.

The diagnosis was angina pectoris, syphilitic aortitis and aortic regurgitation, myocardial degeneration, and complete heart-block (obstructive lesion of the auriculoventricular bundle).

The patient died of heart disease seven and a half months after examination.

This remote localized posterior pain distribution without radiation is unusual. The third, fourth, fifth, and sixth dorsal segments were involved (see Fig. 96).

Case IV (205,922). Mr. T., aged seventy-four, complained of griping pain limited to the interscapular region following exertion (Fig. 99). Examination revealed the heart to be slightly enlarged to the left. There was no arhythmia and no murmur. There was marked sclerosis of the peripheral arteries. The systolic blood-pressure was 165, the diastolic 85. The electrocardiogram showed a rate of 79, with sinus rhythm and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis.

The pain distribution in this case is identical with that in Case IV.

Case V (125,332). Mr. C., aged fifty-four, presented himself for examination complaining of pain, beginning in the left scapular region and radiating through to the front. He had suffered from this pain for two years, and recently the attacks had occurred more frequently (Fig. 100).

The heart was enlarged to the left (? by 15 cm.). No arhythmia and no murmurs were noted. The systolic blood-pressure was 146, diastolic 90. The electrocardiogram showed a rate of 66, with sinus bradycardia, slurring of the initial ventricular complex Q R S in Derivation II, negativity of the final ventricular T wave in Derivation III, and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis.

This patient died of peritonitis four months after examination. This is an unusual pain distribution, in that the origin was posterior with an anterior radiation. The left second, third, fourth, fifth, and sixth dorsal segments were involved.

Case VI (239,215). Mr. R., aged fifty-five, complained of sharp stabbing pain of one and a half years' duration, limited to the right mammary region. The attacks were precipitated by effort (Fig. 101). The heart was markedly enlarged to the

left (2 by 20 cm.). Cardiac action was rhythmic. A systolic murmur was audible over the aortic area and the aortic second tone was accentuated. Sclerosis of the peripheral arteries was definite. The systolic blood-pressure was 198, the diastolic 105. The electrocardiogram showed a rate of 86, with sinus rhythm, notching of the initial ventricular complex Q R S in Derivation II, and negativity of the final ventricular T wave in combined Derivations I and II.

This negativity entails a cardiac mortality of 67.3 per cent. in four and a half years. Preponderance of the left ventricle was present.

The diagnosis was angina pectoris, with sclerosis of the aorta, and coronary sclerosis.

This pain distribution is unusual in being dextral and unassociated with radiation. The right half of the third, fourth, and fifth dorsal segments were involved (see Fig. 95).

Case VII (218,457). Mr. S., aged fifty-eight, gave a history of severe cramping pain, arising in the left hand and forearm and radiating to the right and left chest. This was first noticed two and a half years before. The attacks were brought on by exertion and were associated with dyspnea and a feeling of cold (Fig. 102).

The heart was not enlarged, and there was no murmur or arhythmia. The systolic blood-pressure was 126, the diastolic 108. The electrocardiogram showed a rate of 90, with sinus tachycardia, slurring of the initial ventricular complex Q R S in Derivation I, and preponderance of the left ventricle and negativity of the final ventricular T wave in combined Derivations II and III. This T wave negativity is associated with a cardiac mortality of 25.9 per cent. in four and a half years.

The diagnosis was angina pectoris, with coronary sclerosis.

The patient died in an anginal seizure four months following the examination. The area of pain originating in the left hand and forearm with the bilateral thoracic radiation is extremely unusual. The nerve paths involved were components of the outer and inner cords of the brachial plexus, the posterior cord remaining uninvolved. The nerves were the median, ulnar,

Fig. 102.

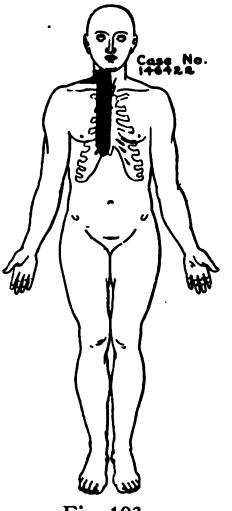


Fig. 103.

Fig. 104.

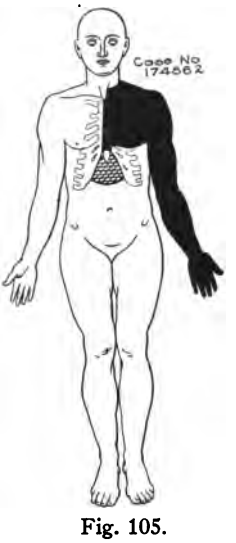


Fig. 105.

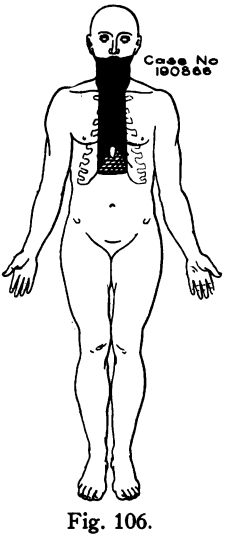


Fig. 106.

Figs. 102–106.—The shaded areas in the figures represent the region of the origin of pain, and the solid black areas the distribution of pain.

musculocutaneous, and internal cutaneous. The radiation involved the second to the eighth dorsal segments inclusive (see Figs. 95, 96).

Case VIII (146,422). Mr. W., aged fifty-four, sought examination for pain which began six years before. The pain, which was described as a severe ache, originated in the right side of the neck and radiated along the right border of the sternum. The attacks were induced by exertion, particularly in cold weather. Dyspnea and a sense of chilliness were constant accompaniments (Fig. 103).

The heart was slightly enlarged to the left (? by 10 cm.). No murmurs were audible. A slight respiratory arhythmia was noted. The aortic second tone was accentuated. The systolic blood-pressure was 184, the diastolic 72. The electrocardiogram showed a rate of 65, with sinus arhythmia and preponderance of the left ventricle. This is a very unusual regional pain distribution. The sensory nerves of the neck are largely derived from the third cervical nerve. This nerve, together with the second cervical, communicates with the descending hypoglossal nerve through the loop termed the "ansa hypoglossi." The ansa hypoglossi, in turn, gives rise to filaments communicating with the vagus, cardiac, and phrenic nerves. In this manner the abnormal stimuli of angina pectoris may aberrate to the neck (see Fig. 95).

Case IX (242,391). Mr. C., aged sixty-nine, complained of aching pain of five years' duration located in both arms, which were diffusely involved. The pain was not experienced in any other portion of the body; it occurred on exertion, particularly after eating (Fig. 104). The heart was enlarged to the left (? by 11 cm.). No arhythmia and no murmurs were present. The peripheral arteries were definitely thickened. The systolic blood-pressure was 170, the diastolic 115. The electrocardiogram showed a rate of 75; with sinus rhythm, notching of the initial ventricular complex Q R S in Derivation III, and preponderance of the left ventricle.

The diagnosis was angina pectoris, with coronary sclerosis and hypertension. The patient died of heart disease twenty months after examination. The unusual feature in this case was the localization of pain in the arms. This is a typical brachial plexus distribution in which the fifth, sixth, seventh,

and eighth cervical and first dorsal segments were involved. The probability is that the intercostohumeral nerve (second dorsal) was uninvolved, but the arm was too diffusely involved to determine an isolated area (see Figs. 95, 96).

Case X (173,245). Mr. H., aged sixty-six, gave a history of pain, bursting in character, located in both arms. The pain did not radiate. He had been suffering from this for seven years. The pain always followed exertion and was relieved by resting (Fig. 104). The heart was definitely enlarged to the left (? by 15 cm.). An extrasystolic arhythmia was present. No murmurs were heard. The systolic blood-pressure was 115, the diastolic 60. The electrocardiogram gave a rate of 83, with sinus rhythm, notching and broadening of the initial ventricular complex Q R S in all derivations, T wave negativity in Derivation I, and preponderance of the left ventricle.

The bizarre Q R S complex involving all derivations of the electrocardiogram is of marked prognostic significance, entailing a high and early mortality.[4]

A diagnosis was made of angina pectoris and coronary sclerosis.

This patient died of heart disease five months after examination. The pain distribution in this case is identical with that in Case IX.

Case XI (174,562). Mr. R., aged twenty-four, complained of attacks of aching pain beginning in the pit of the stomach, radiating into the left chest, involving the upper two-thirds, and then radiating into the left arm (Fig. 105). The history dated back three years. The attacks were associated with a sense of fulness and accompanied by perspiration, and were induced by exertion, particularly after eating. The attacks had occurred daily of late. Syphilis was denied. The patient had had several attacks of rheumatic fever.

The heart was enlarged (3.5 by 13.5 cm.). There was no arhythmia present and a loud blowing diastolic murmur was heard over the entire cardiac area, being most marked along the left sternal border. Capillary and water-hammer pulse and femoral pistol-shots were present. The systolic blood-

pressure was 148, the diastolic 32. The Wassermann reaction was negative. The electrocardiogram showed a rate of 86, with sinus rhythm, notching of the initial ventricular complex Q R S in Derivations II and III, T wave negativity in Derivation I,[5] and preponderance of the left ventricle.

The diagnosis was angina pectoris and chronic rheumatic endocarditis, with aortic regurgitation.

The patient died of heart disease nineteen months after examination. The unusual feature in this case is the abdominal pain origin. The abnormal stimulus evidently involves the upper dorsal segments first.

Case XII (190,866). Mr. D., aged forty-nine, came for examination complaining of attacks of pain of three years' duration. The pain, described as being severe and boring in character, began in the pit of the stomach and radiated into the middle chest, neck, and lower jaws (Fig. 106). It constantly occurred following exertion, especially after eating, and was relieved by rest.

The heart was slightly enlarged to the left (3 by 11 cm.). No arhythmia and no murmurs were noted. The systolic blood-pressure was 84, the diastolic 62. The electrocardiogram showed a rate of 86, with sinus rhythm, slurring of the initial ventricular complex Q R S in Derivation I, and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis.

The patient died of heart disease fifteen and a half months after examination. As in Case XI, the origin of pain was abdominal, but the radiation was most unusual, extending high enough to involve the mandibular branch of the trigeminus.

Case XIII (244,568). Mrs. A., aged fifty-two, complained of severe aching pain under the right costal margin, radiating through to the back. The origin and radiation of the pain was so typical of gall-bladder disease that the patient was referred to the clinic with this diagnosis (Fig. 107). The story, however, did not ring true for gall-stones, as the patient stated that the attacks were always induced by effort. The pain had been present for three months, but breathlessness following unusual exertion had been noted for thirty years.

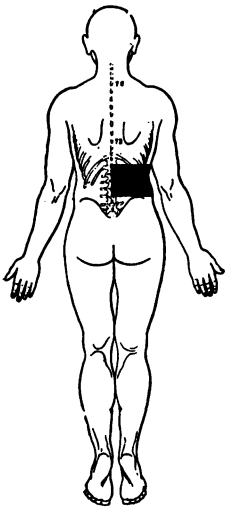
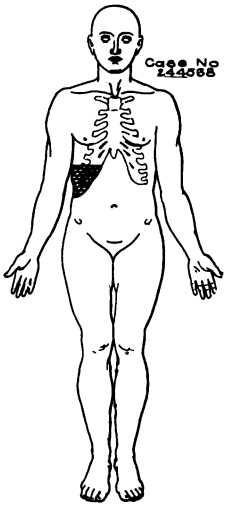


Fig. 107.



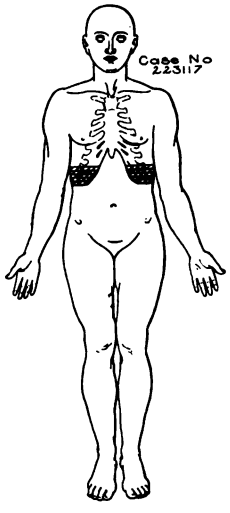


Fig. 108.

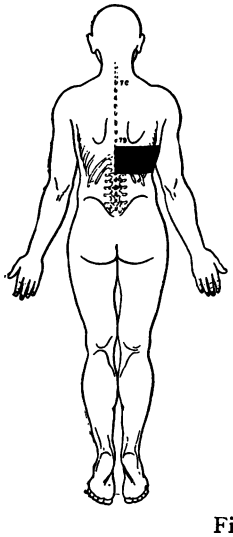


Fig. 109.

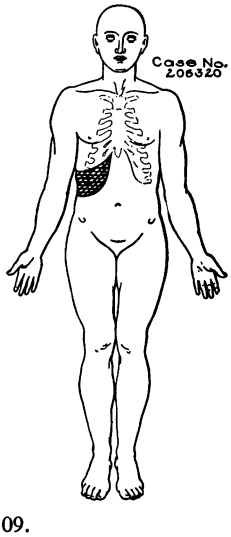


Fig. 110.

Figs. 107–110.—The shaded areas in the figures represent the region of the origin of pain, and the solid black areas the distribution of pain.

The heart was slightly enlarged (3.5 by 11.5 cm.). The pulse was completely arhythmic, and a blowing systolic murmur

was heard over the apex. The systolic blood-pressure was 130, the diastolic 70. The electrocardiogram showed a rate of 127, with auricular fibrillation, ventricular premature contractions, and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis (?), chronic mitral endocarditis with regurgitation, and chronic myocarditis with auricular fibrillation. Auricular fibrillation is extremely rare with angina pectoris, occurring in only 1.9 per cent. of cases.[6] In this case a history of thirty years of heart trouble preceding the development of anginal seizures indicates a primary endocardial and myocardial invasion and probably recent obliterative intrinsic vascular changes. The patient died of heart disease one year after examination. The lower dorsal segments on the right side were involved in this unusual pain manifestation (see Figs. 95, 96).

Case XIV (233,117). Mr. B., aged fifty-three, gave a history of attacks of pain of one year's duration. The discomfort was described as a pressure pain associated with a sense of fulness under both costal margins (Fig. 108). The pain did not radiate. The attacks of pain were induced by exertion.

The heart was not enlarged (3 by 9 cm.); no arhythmia and no murmurs were noted. The systolic blood-pressure was 130, the diastolic 78. The electrocardiogram showed a rate of 69 with sinus bradycardia, slurring of the initial ventricular complex Q R S in Derivation III, and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis.

The bilateral costal distribution of pain without radiation is unusual. The eighth and ninth dorsal segments were involved.

Case XV (206,320). Mr. D., aged fifty-six, presented himself for examination complaining of attacks of pain which had been present for one year. The pain, which was pressing in character, began under the right costal margin and radiated through to the back at a slightly higher level (Fig. 109). The attacks of pain followed exertion.

Examination revealed the heart to be slightly enlarged to the left (3.5 by 11 cm.). No arhythmia and no murmurs were present. The systolic blood-pressure was 122, the diastolic

80. The electrocardiogram showed a rate of 86, with sinus rhythm, notching, and broadening of the initial ventricular complex in all derivations,[4] T wave negativity in Derivation I,[5] and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis. The patient died of heart disease five months after examination. The pain distribution in this case was similar to that in Case XIII.

Case XVI (174,323). Mrs. E., aged fifty-two, complained of severe boring pain beginning in the pit of the stomach and radiating down the left arm. The attacks followed exertion, especially soon after eating. This complaint had been present for two years (Fig. 110). The heart was slightly enlarged to the left (? by 10 cm.). No arhythmia and no murmurs were present. The systolic blood-pressure was 148, the diastolic 86. The electrocardiogram showed a rate of 94, with sinus tachycardia, and T wave negativity in combined Derivations II and III.[5]

The diagnosis was angina pectoris, with coronary sclerosis.

The patient died of heart disease shortly after examination. The pain origin was unusual in being abdominal, although the radiation is typical.

Case XVII (232,844). Mr. M., aged fifty-one, gave a history of attacks of pain during the last year. The pain was severe and cramping in character, beginning in the pit of the stomach, radiating to both sides and through to the back, involving a localized area to a point a little below the scapulæ (Fig. 111). The attacks followed exertion, particularly soon after a meal.

The heart was not appreciably enlarged (3.5 by 9.5 cm.). No arhythmia and no murmurs were noted. The systolic blood-pressure was 130, the diastolic 86. The electrocardiogram showed a rate of 56, with sinus bradycardia and preponderance of the left ventricle. The diagnosis was angina pectoris, with coronary sclerosis. This patient died in an anginal attack twenty months after examination.

The fourth, fifth, sixth, seventh, and eighth dorsal segments are involved in this pain distribution (see Figs. 95, 96).

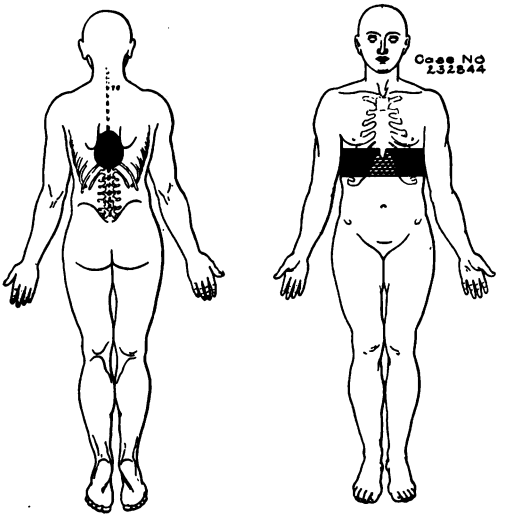


Fig. 111.

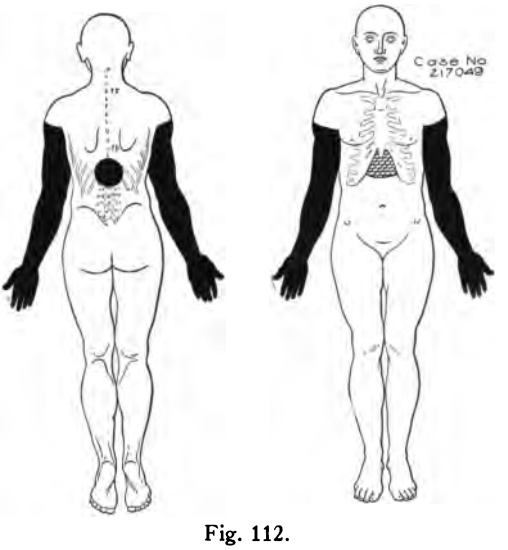


Fig. 112.

Figs. 111, 112.—The shaded areas in the figures represent the region of the origin of pain, and the solid black areas the distribution of pain.

Case XVIII (217,049). Mr. A., aged sixty-three, complained of attacks of severe sickening pain, beginning in the pit of the

stomach, radiating through to a localized area in the back and into both arms (Fig. 112). The history dated back nine months. The pain followed effort and eased with rest.

Examination of the heart revealed no arhythmia and no murmurs. The systolic blood-pressure was 157, the diastolic 90. The electrocardiogram showed a rate of 67, with sinus bradycardia.

The diagnosis was angina pectoris, with coronary sclerosis. The pain origin being abdominal is unusual, but the radiation is not uncommon. The nerve paths involved have been discussed previously.

Case XIX (177,039). Mrs. M., aged sixty-six, volunteered a history of attacks of pain during the last year. The pain, coming on suddenly, originating in the pit of the stomach and radiating across the lower chest and through to the back, was oppressive in character (Fig. 113). The attacks were induced by exertion.

Examination of the heart revealed no arhythmia or murmurs, but the sounds were distant and lacked definition and differentiation. The systolic blood-pressure was 115, the diastolic 85. The electrocardiogram showed a rate of 88 with sinus rhythm, notching, and broadening of the initial ventricular complex in all derivations,[4] T wave negativity in Derivation I,[5] and left ventricular preponderance.

The diagnosis was angina pectoris and coronary sclerosis.

The patient died of heart disease soon after examination.

The seventh and eighth dorsal segments were involved in this peculiar pain distribution (see Figs. 95, 96).

Case XX (173,600). Mr. N., aged sixty-six, came for examination, complaining of attacks of pain of five years' duration. The pain, severe and griping in character, began in the pit of the stomach, radiated across the upper abdomen at the umbilical level, and into both arms, involving the left arm diffusely and the ulnar aspect of the right, and radiating through to a localized area in the back (Fig. 114). The attacks were precipitated by effort, especially soon after a meal. The cardiac examination revealed nothing of importance.

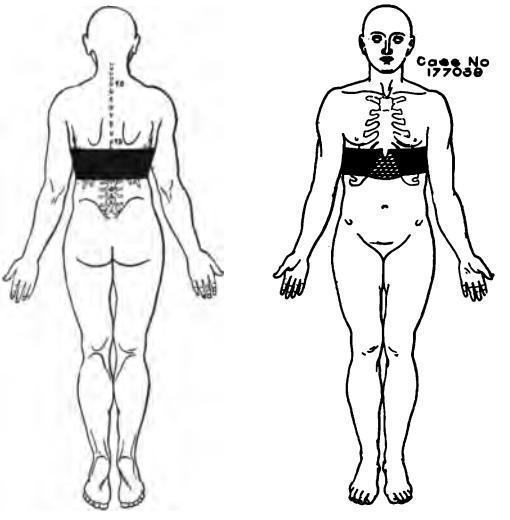


Fig. 113.

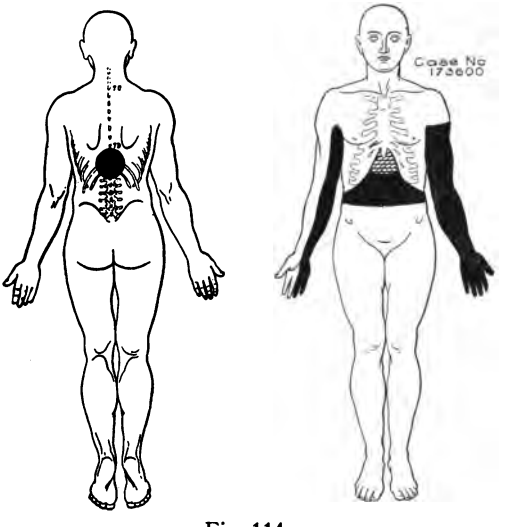


Fig. 114.

Figs. 113, 114.—The shaded areas in the figures represent the region of the origin of pain, and the solid black areas the distribution of pain.

The systolic blood-pressure was 150, the diastolic 98. The electrocardiogram showed a rate of 69, with sinus bradycardia.

The diagnosis was angina pectoris, with coronary sclerosis.

This patient died in an anginal attack two and a half months after examination. Similar pain distributions have been discussed in previous cases and need not be repeated here (see Figs. 95, 96).

Case XXI (193,470). Mr. O., aged sixty-two, complained of severe attacks of pain of two months' duration. A violent pressure pain was located in the upper abdomen and did not radiate (Fig. 115). The attacks followed exertion and gradually

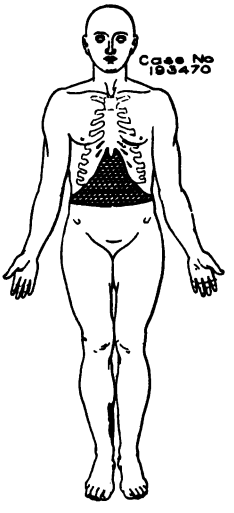


Fig. 115.

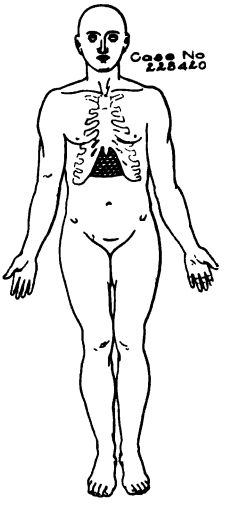


Fig. 116.

Figs. 115, 116.—The shaded areas in the figures represent the region of the origin of pain, and the solid black areas the distribution of pain.

waned after about two hours of rest. The heart was definitely enlarged to the left (? by 15 cm.). No arhythmia and no murmurs were recorded. The systolic blood-pressure was 150, the diastolic 100. The electrocardiogram showed a rate of 68, with sinus bradycardia, T wave negativity in Derivation I,[5] and left ventricular preponderance.

The diagnosis was angina pectoris, with coronary sclerosis.

The patient died of heart disease soon after examination.

The diffuse upper abdominal pain in this case was unusual

and emphasized the possibility of confusing such a pain distribution with some acute surgical abdominal disease.

Case XXII (228,420). Mr. G., aged sixty-six, came for examination on account of attacks of pain beginning one year before. The pain was boring in character and located in the pit of the stomach (Fig. 116). Associated with the pain was a sense of smothering and choking. The attacks constantly followed exertion, especially when the patient was out in cold weather. Examination of the heart revealed an extrasystolic arhythmia. No murmurs were audible. The heart tones were distant and lacked definition and differentiation. The systolic blood-pressure was 190, the diastolic 90. The electrocardiogram showed a rate of 106, with ventricular premature contractions and notching, and broadening of the initial ventricular complex Q R S in all derivations.

The diagnosis was angina pectoris, with coronary sclerosis.

The patient died of heart disease eleven months after examination.

This regional pain distribution has already been discussed.

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CLINIC OF DR. GEORGE B. EUSTERMAN

A Case of Delayed Postoperative Obstruction of the Proximal Loop of the Jejunum from Adhesions and a Description of the Attendant Phenomena Including Gastric Tetany. Discussion of the Discrepancy Between Clinical and Roentgen-ray Observations on Motor Function. Summary.

CASE I (353,615). Mrs. O. G. B., aged thirty-one years, entered the Clinic March 28, 1921. She complained of rather persistent vomiting and loss in weight and strength. She had been married for fourteen years, was the mother of 2 healthy children, and had had four abortions, probably induced. The family history was practically negative with the exception that the patient's mother was neurasthenic and suffered from chronic recurring hemicrania. The patient had been subject to periodic attacks of migraine, usually preceding menstruation and relieved by vomiting. She had also suffered from chronic constipation complicated by a cathartic colitis; the former had been more marked since the birth of her first child seven years before. In September, 1920 a surgeon in a small Canadian city had performed a posterior gastrojejunostomy following a Roentgen-ray examination in which a diagnosis of duodenal ulcer had been made. This procedure was confirmed by a letter from the patient's family physician, who had witnessed the operation. The patient had vomited repeatedly for about the first five days after the operation, the vomitus consisting of grumous material at the outset, followed by large amounts of bile. The gastric disturbance was controlled by one lavage, and the patient was free from gastric trouble until December, 1920, when obstructive symptoms appeared almost daily. They were mildly progressive, accompanied by hunger, visible gastric peristalsis, incipient tetanic manifestations, and marked

loss in weight and strength. Restricting the diet to milk at frequent intervals for weeks at a time afforded little relief. Gastric analysis had not been made and the preoperative clinical study had been superficial and brief. Strangely enough there had been complete subsidence of the headaches since the onset of the gastric disturbance.

Examination showed the patient to be fairly well developed, but emaciated; her normal weight was 110 pounds; she now weighed 85 pounds. There were no objective findings of importance, although a small ventral hernia, hypotension, traces of albumin in the urine, and occasional hyaline casts were recorded. The Wassermann reaction was absent in the blood-serum. A cursory neurologic examination did not reveal abnormalities. A modified Riegel motor meal eaten at 6 o'clock in the evening was vomited about 5 in the morning. One hour after an Ewald meal the same morning a filtrate measuring 460 c.c. and containing considerable bile was recovered. The total acidity was 14 (in terms of tenth-normal sodium hydroxid) and the free hydrochloric acid was 8. On fluoroscopic examination the stomach was found to be considerably dilated, with fair tonus and hyperperistalsis; a moderate six-hour barium retention was present, but the stoma could not be seen. There was no Roentgen-ray evidence of an ulcer either in the duodenal cap or in the body of the stomach.

The patient was sent to the hospital for further study. After two weeks of complete rest in bed on soft general diet, with enteroclysis and nightly aspirations, the patient's vomiting was controlled and she gained 6 pounds in weight. The gastric contents frequently measured from 1000 to 1350 c.c., with some food remnants, considerable biliary elements, a high tryptic index, but no blood, gross or occult. Blood was not found in the feces on repeated examination. Free hydrochloric acid was invariably 0; the total acidity varied from 18 to 52. Often the upper abdomen was moderately distended and gastric peristalsis without pain was visible. The patient said she had been aware of the latter since the onset of the vomiting. She also complained of numbness and twitching sensations in the

hands and feet. At times a hard evanescent mass could be palpated in the middle of the epigastrium. April 12th the aspiration of the gastric contents nine hours after a motor meal revealed 500 c.c. of a bile-stained fluid with some gross food remnants; the total acidity was 26, the free hydrochloric acid was 6. Two days later fluoroscopic examination did not show retention of the opaque meal after six hours, nor the gastro-enterostomy. These motor studies apparently precipitated a typical attack of gastric tetany on the afternoon of April 16th. Pedal spasm, main d'accoucheur, a purplish thick tongue which interfered with speech, a state of apprehension, and distress from the subjective sensations in the extremities were noted by the house physician. Chvostek's sign and Trousseau's phenomenon were easily elicited by me twenty minutes after the subsidence of the more acute phenomena. I observed that the stomach was markedly distended and plainly outlined against the abdominal wall. By means of a Rehfuss tube 1050 c.c. of greenish fluid chyme were removed, followed by marked relief and a gradual subsidence of the gastric distention. Estimation of the plasma carbonates (Van Slyke) indicated a marked alkalosis. A 5 per cent. glucose enteroclysis by the drip method and generous doses of calcium lactate by mouth resulted in a speedy recovery from this alarming complication, so that on April 24th the patient could be transferred to the surgical service.

To summarize, we were dealing with a patient in whom the clinical evidence for ulcer had been practically absent prior to operation, and the diagnosis had been based entirely on a Roentgen-ray examination. This is not an unusual practice, and it cannot be too strongly condemned. The immediate postoperative convalescence was stormy, a fact of diagnostic significance in problems dealing with postoperative sequelæ. The later symptoms were more urgent, distinctly gastric, and quite different from the symptoms for which the patient had originally sought relief. This argued for the fact that surgical interference in some mechanical way was the cause of the obstruction, dilatation, regurgitant vomiting, and finally, gastric

tetany. Inability to visualize the gastro-enterostomy opening is, in our experience, most often due to the fact that a gastro-enterostomy had not been performed. Gastrojejunal ulcer by virtue of intermittent spastic closure, or rarely by complete cicatricial contraction of the stoma, may be a second cause for failure to see the opening. A third reason may be obstruction either of the proximal or of the distal jejunal loop at or near the stoma, usually the result of technical error or surgical accident. Moynihan has described the manner in which the last type of complication may supervene:

"The anterior or the posterior operation has been performed, and a long jejunal loop has been left. This loop may, with difficulty, be emptied; it may become 'water-logged,' and an obstruction may develop at the afferent opening into the stomach. 'Regurgitant vomiting' occurs only to be relieved by lavage, or in severe cases by the performing of an entero-anastomosis, which checks it at once.

"With a short or a long loop the efferent piece of jejunum has been blocked as a consequence of a kink, or from adhesions, between the intestine on the one side, and the abdominal wall, omentum, transverse colon or mesocolon, and loops of small intestine on the other. Regurgitation occurs here also. Regurgitant vomiting means high intestinal obstruction.

"A short loop posterior gastro-enterostomy had been performed. At the time when the jejunum was lifted up to oppose to the stomach before suture adhesions were found binding it to the under surface of the transverse mesocolon, an exaggeration of the ligament of Treitz. These were divided and a raw surface left on the jejunum, proximal to the opening made to anastomose with the stomach. Adhesions then formed and caused obstruction of the proximal part of the jejunum between the duodenojejunal flexure and the opening into the stomach.

"The jejunum has been rotated round its longitudinal axis at the time when it has been approximated to the stomach. This twist may be quite enough to cause an obstruction."

The six-hour barium motor meal is a sensitive test for gastric motility on which the clinician places considerable reliance.

In the presence of organic stenosis there is a fairly constant parallelism between six-hour barium retention and the food remnants obtained ten or twelve hours after the administration of a Riegel motor meal. This patient, strangely enough, had many clinical signs of high intestinal obstruction, confirmed by a nine-hour Riegel motor meal, but, as I have pointed out, the second barium motor meal had all passed out of the stomach and jejunal loop before the end of the sixth hour. The retarding influence of nausea, migraine, anorexia, and morphin was not a factor. Such discrepancies between food and barium tests for gastric motility had been noted before under similar circumstances. I believe that in the presence of much fluid, transudate, or hypersecretion the more reliable index of gastric motility is obtained by the old time-honored motor meal. From a summation of all the evidence a diagnosis was made of a nonulcerative, postsurgical obstruction at or just below the level of the stoma, with marked gastrectasia.

April 26, 1921 a secondary operation was performed (C. H. Mayo). The stomach was found to be greatly dilated, the pylorus open, and there was no evidence of previous ulceration in the stomach or duodenum. The gastro-enterostomy was large and patent, and easily admitted three fingers. Beyond this there were extensive adhesions, producing a marked angulation of the proximal loop, which on freeing the adhesions was found to be twisted and turned to the right. An enteroanastomosis of the proximal loop to the distal loop was quickly made. The patient recovered uneventfully; she has gained 20 pounds in weight in three months and is in good health.

The Formation of a Chronic Penetrating Ulcer of the Stomach Following Successful Gastrojejunostomy for an Obstructing Duodenopyloric Ulcer; Rarity of Such a Sequel. Typical Ulcer Syndrome Despite Consistent Achlorhydria. Factors Which May Give Rise to a Constant Absence of Hydrochloric Acid in the Presence of Chronic Benign Ulcer. Observations on the Etiology and Mechanism of the Production of Pain in Ulcer.

CASE II (147,732). Mr. McD., aged forty-nine years, first entered the Clinic December 11, 1915 with the complaint typical of duodenal ulcer of two years' duration and pyloric obstruction clinically of five months' duration.

Aspiration twelve hours after a Riegel motor meal showed considerable food residue and some sarcinæ; the total acidity, in terms of tenth-normal sodium hydroxid solution, was 42 and the free hydrochloric acid was 30. A barium motor meal revealed a small residue after six hours. On fluoroscopic examination the stomach was found to be large, with active peristalsis, moderately mobile, orthotonic, and of fish-hook form. There was a definite filling defect of the pylorus and of the lesser curvature with an accessory pocket which persisted on the screen and on the plates. A Roentgen-ray diagnosis was made of chronic perforating ulcer at the pylorus with obstruction.

December 20, 1915, after a week of restricted diet, enteroclysis, and gastric lavage, a posterior gastrojejunostomy was performed (C. H. Mayo). A perforating ulcer of the duodenum was found extending into the pylorus. The pylorus was almost completely closed. A retrocecal distended appendix was also removed.

June 15, 1921, five and a half years later, the patient returned to the Clinic because of a recurrence of painful symptoms. He stated that for three months following his operation he had enjoyed excellent health. Then, following a generous meal including pie made of preserved cranberries, he was seized

with marked epigastric distress, emesis, and diarrhea. This distress persisted daily from July to November, 1916. The diarrhea was then succeeded by marked constipation, which has persisted. He had intermittent brief periods of epigastric pain and gaseous distress throughout the course of the large bowel (colitis), which appeared regularly several hours after meals, but was most severe usually from 4 to 6 P. M. The symptoms were consistently relieved by food, alkalies, lavage, emesis,

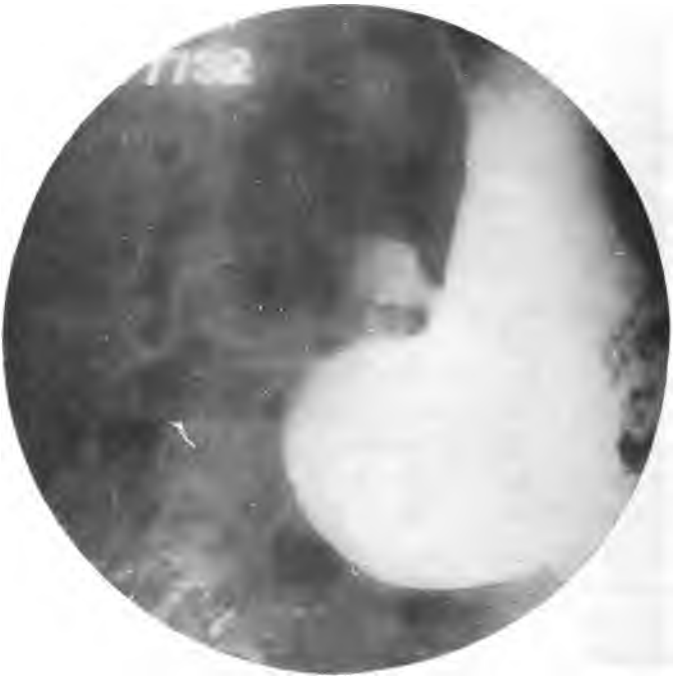

Fig. 117.—(Case 147,732.) Penetrating ulcer of the lesser curvature. Gastroenterostomy patient.

posture, and local heat. In June, 1920 he had a more marked exacerbation which lasted for three months. Vomiting and marked temporary loss of weight were additional features. There has been no gross hemorrhage at any time.

The only noteworthy finding on physical examination was diffuse moderate tenderness limited to the middle of the epi-

gastrium. The hemoglobin was 72 per cent., the red cell count 4,490,000. The scar of the previous laparotomy was firm. Gastric analysis twelve hours after a Riegel meal and one hour after an Ewald meal revealed total acidity 10, free hydrochloric acid 0, a trace of occult blood, a small amount of mucus, bile ++, and total amount of filtrate 30 c.c. A complete fractional analysis disclosed an absence of free hydrochloric acid throughout the digestive cycle. Traces of blood were irregularly present

Fig. 118.

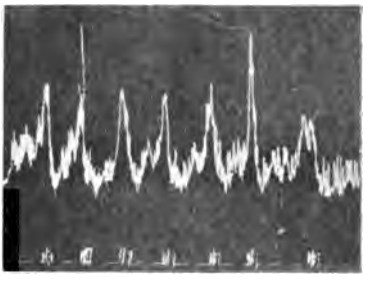

Fig. 119.

Figs. 118, 119.—(Case 147,732.) Kymographic records of the contractions of the stomach after a test-meal. During the first four hours after eating the patient did not have pain, and the kymograph revealed only slight tonus variations (Fig. 118), but four and a half hours after eating the stomach became more active and definite peristalsis was recorded (Fig. 119). Intermittent gnawing, cramp-like pains were experienced; in almost every instance they were synchronous with the peristalsis. During the course of the tracing 15 to 20 c.c. of gastric contents were aspirated through the Rehfuss tube every half-hour, but free hydrochloric acid was not present on successive titrations of the contents removed fractionally.

in the feces. Fluoroscopic examination showed the stoma to be functioning normally, at least two-thirds of the barium leaving by this opening, but both on the screen and roentgenogram a defect on the lesser curvature characteristic of a penetrating ulcer was plainly in evidence. A small barium retention after six hours was also recorded (Fig. 117).

Observation at the hospital confirmed the patient's statements with regard to the severity, the time of appearance, and the mode of control of the pain. On repeated aspiration during the height of his discomfort the gastric contents rarely

exceeded 50 c.c.; food residues were absent four hours after alimentation. Achlorhydria was constant, but simple aspiration, with or without gastric lavage, emesis, eating, or alkalies, gave constant relief. During a typical period of trouble kymographic tracings were made by Dr. Hardt. As a result of this investigation it seemed reasonable to conclude that the pain was peristaltic in nature (Figs. 118, 119).

June 27, 1921 a second laparotomy was performed (C. H. Mayo). A chronic indurated ulcer (3 by 1.5 by 1 cm.) about 5 cm. above the pylorus was excised, and the opening closed in an opposite direction with three rows of chromic catgut sutures. The original duodenal ulcer had healed completely, and the gastro-enterostomy was found to be normal and patent. Microscopic examination of the excised ulcer did not reveal evidence of malignant changes. The patient made an uneventful recovery.

DISCUSSION

This case is of interest for two reasons: first, because of the apparent occurrence of a new gastric ulcer in the presence of a normal functioning gastro-enterostomy plus achlorhydria, and, second, because of a typical benign ulcer syndrome in the persistent absence of free hydrochloric acid. It might be argued that the ulcer was present at the time of the original operation and had been overlooked by the surgeon; in fact, we have no reliable evidence to disprove such contention. Chronic gastric ulcers, especially those with marked induration and remote from the pylorus, frequently have been known to persist after gastro-enterostomy alone, the operative procedure being followed by only brief periods of relief. Recently a case has come under my observation in which a superficial gastric ulcer failed to heal following gastro-enterostomy, but progressed under the most favorable circumstances of motility and gastric chemism, which in our experience is a rare occurrence (Figs. 120, 121). In contrast to this, gastric ulcers, especially those in earlier stages of chronicity, have been observed to disappear under successive fluoroscopic examination during medical treatment in the hospital, and eventually to heal permanently

Fig. 120.

Fig. 121.

Figs. 120, 121.—(Case 231,960.) Mrs. W. O'C., aged forty-seven years, entered the Clinic May 21, 1918. She had had a typical gastric ulcer syndrome of the intermittent type for twenty years. There were pain and tenderness in the left epigastrium with lateral and posterior radiation. The total acidity was 74, the free hydrochloric acid 58, the filtrate 50 c.c. May 22, 1918 fluoroscopic examination revealed a niche high on the lesser curvature. The roentgenogram showed an incisura only opposite the niche.

Laparotomy May 27, 1918 (E. S. Judd) disclosed "a small superficial ulcer of the lesser curvature and anterior wall. Because of its high situation it was impossible to reach the ulcer and successfully excise it. A posterior gastro-enterostomy was done."

August 8, 1921 the patient re-entered the Clinic. She had had relief for two months following operation; since then the recurrence of the old symptoms has become progressively more severe. Gastric analysis (fractional) showed total acidity 20 and free hydrochloric acid 0 throughout the digestive cycle.

August 11, 1921 a roentgenogram revealed an ulcer high on the lesser curvature and the gastro-enterostomy free.

by thorough management and with the patient's co-operation. But it might be argued with greater conviction that the ulcer, in all probability, did not exist before the operation, since the surgeon could hardly have failed to discover a calloused, indurated ulcer. The gastro-enterostomy with the resulting achlorhydria usually results in the complete resolution of the lesion. Moreover, we have had eight previous similar experiences confirmed by secondary operation, in the majority of which there was no reason to suppose that a gastric ulcer was present at the time of the original operation. Naturally, speculation was rife as to the possible etiologic factor in these cases. Syphilis or focal infection, in our experience, especially the latter, should be carefully excluded as causative factors in such sequelæ.

The formation of a new ulcer may be the cause of severe gastro-enteric hemorrhage when such a complication had not obtained in the original ulcer. In a previous contribution, however, I emphasized the fact that such hemorrhage was likely to have its origin in an ulcerative process at or beyond the stoma, that is, in a gastrojejunal or jejunal ulcer. Many hemorrhages, in my experience, have an unexplainable origin, but it is rare that a duodenal ulcer gives rise to hemorrhage after gastrojejunostomy when gross bleeding had not occurred prior to operation.

The combination of a characteristic ulcer complex in the presence of a consistent achlorhydria is not so unusual. The association of consistent gastric anacidity with chronic benign ulcer of the stomach or duodenum is exceedingly interesting clinically and can invariably be explained by systemic or local causes. The coexistence of grave constitutional disease, such as pulmonary or intestinal tuberculosis, chronic renal disease, uremia, pernicious anemia, pellagra, sprue, the metabolic diseases, such as gout, diabetes, or the chronic infectious states, such as the arthritides or severe oral sepsis, may exert a profound influence on gastric secretion. Gastric chemism is greatly influenced by the state of the patient's general health, and because of this we are beginning to realize the greater importance of subacidity rather than hyperacidity. In the absence of

reliable evidence of systemic disease lesions of the accessory digestive tract, especially chronic cholecystitis or chronic pancreatitis, may be responsible for the perverted chemistry. Other equally important local causes are the possibility that the ulcer may be syphilitic or undergoing malignant degeneration. In 66 cases of satisfactorily proved organic gastric syphilis gastric anacidity was present in more than 80 per cent., but the involvement was invariably diffuse and extensive, rarely circumscribed, simulating carcinoma closely in this respect. For some unexplainable reason certain duodenal and pyloric ulcer-bearing patients with hyperacidity or hypersecretion following gastrojejunostomy may have constant achylia with or without disturbed gastric or intestinal function. In any event, it is necessary to repeat a gastric analysis, as a complete psychical achylia may be present on the first examination of patients whose gastric contents subsequently are found to have a marked degree of hyperacidity. That some ulcers may be purely infectious, metabolic, or arteriosclerotic in their origin may explain some of the vagaries of gastric chemistry.

Crispin has reported 11 cases of duodenal ulcer confirmed by operation, in which there was achlorhydria. His observations are probably open to the criticism that they were based on single analyses of the gastric contents; moreover, the analyses were not made during the period of discomfort. I believe, however, that the majority of these cases would have shown achlorhydria consistently. In our patients it was shown that free hydrochloric acid was persistently absent, even during the height of the pain, and that motor function was good.

For many years Sippy has taught and published his views that pain in the presence of an uncomplicated ulcer is always associated with an adequate acidity and an adequate amount of gastric juice. In other words, the corrosive or irritating action of the hydrochloric acid was, at least by implication, necessary to the mechanism of the production of pain. While this is often the case, it is not invariably so. We have seen relief afforded to such a patient by the same agents which would have given relief in the presence of the usual hyperacidity and

hypersecretion. Such observations tend to support the claims of Hertz, Carlson, Ginsberg, Hardt, Poulton, and others that the cause of the pain is the result of heightened intragastric pressure, distention, and peristalsis rather than the corrosive action of the hydrochloric acid of the gastric juice directly on the ulcer-bearing area. Homans, however, by applying the methods of investigation used by Carlson, Ginsberg, and Hardt, could not confirm their observations. In the presence of a proved gastric or duodenal ulcer he showed that powerful contractions of the fundus may not cause pain, and that pain may occur independently of any muscular activity of the fundus. These data impress one with the fact that in order to promote healing it is not so necessary to effect complete neutralization of the free hydrochloric acid as it is to give bland food often in small amounts combined with alkalies and proper rest. On the other hand, my experience in several hundred cases has taught me that complete neutralization of the hydrochloric acid in ulcer-bearing patients always is accompanied by complete cessation of gastric pain. Such neutralization also hastens the restoration of gastric motility in inflammatory obstructions at the pylorus as well as resolution of the ulcer area. It is reasonable to assume from repeated clinical observations that hyperacidity, when present, is a link in the chain of factors provoking gastric pain:

"The influence of the chemical reaction of the gastric content on the pylorus is more complicated, but high acidity will intensify and prolong the duodenal reflex contraction of the pylorus as well as induce strong contractions in the duodenum itself. Clinical hyperacidity may in this manner indirectly aggravate the ulcer pains from the contraction of these parts of the alimentary canal, and any measure (protein, food, water, or alkalies) that temporarily lowers gastric acidity will temporarily ease these pains, provided there is sufficient relaxation of the pylorus to allow the weakened gastric content to reach the duodenum" (Carlson).

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PREOPERATIVE MANAGEMENT IN CASES OF GASTRIC RETENTION

DAVID M. BERKMAN

IN an attempt to correlate clinical observations with experimental observations on the phenomenon of the motor function of the stomach, I have reviewed our experiences with gastric retention as encountered and dealt with in a group of surgical conditions of the stomach and duodenum.

Since ordinary text-book classifications are not entirely adequate, the modern conception of the causes of gastric retention should be recapitulated. There are two main groups of cases: (1) actual organic stricture of the pylorus, and (2) functional interference with the motive power of the stomach.

In Group 1 are found, in the order of their frequency, malignant neoplasm, cicatricial stenosis, inflammatory swelling and edema (acute pyloric or duodenal ulcer), adhesions, gross syphilis, and benign tumor. Other lesions, such as tuberculosis, occur so rarely as to be negligible. I shall not consider the congenital form of pyloric obstruction in these observations.

A consideration of Group 2 demands a rather close investigation into our knowledge of the factors in gastric motility. Spasm of the pylorus like that which occurs in cardiospasm is very probably as rare as the latter. Spasm of a rhythmic, intermittent type is a part of the normal function of the pylorus. Food retention, so frequently attributed to pylorospasm, is more likely attributable to derangement of a very delicately co-ordinated relation between peristaltic waves of the stomach and closure of the pyloric sphincter. We are indebted to Wheelon and Thomas for a definite idea of the interrelationship between antral and pyloric muscular contractions. Briefly, they have demonstrated that the sphincter is relaxed during only the

first part of the antral contraction. Constriction of the sphincter begins when the antral wave is at its maximum and supplements this action until the next antral movement is under way. Thus, as Cole has found from Roentgen-ray observations, the pylorus is open only during gastric systole. This fact tends to throw doubt on the theory of acid control, a doubt further strengthened by other experimental work, which demonstrated that fluid taken from the duodenum close to the pylorus and during a discharge from the stomach is alkaline or very weakly acid (Luckhardt, Phillips, and Carlson).

The stomach exhibits a remarkable adaptability and continues to empty itself in the face of various deforming diseases and surgical operations which would seem to have left the originally delicately balanced mechanism in chaos.

Alvarez has observed that the stomach, like the heart, has an extrinsic and an intrinsic nervous mechanism. Owing to the marked difference in the distance to be traversed, synchronous waves passing along the greater and lesser curvatures must travel at different speeds in order to reach the pylorus simultaneously. It is logical to assume that any perceptible shortening of the lesser curvature interferes with the timing of the composite peristaltic wave. In the same manner irritation of the lesser curvature may result in motor difficulty. There are many possibilities of trouble associated with the various diseases of the wall of the stomach which produce ulcerative and infiltrative changes. The lower half of the stomach contains by far the greater part of the gastric musculature which increases in thickness and power as it approaches the pylorus. Motor difficulties are not uncommon following partial gastrectomy for carcinoma at the pylorus, but in such cases the tendency is almost always for improvement for from six weeks to three months after operation. As the stomach does not empty by gravity, this improvement is due to simple development of the musculature of the upper part of the stomach and to some marvelous readjustment of the nervous mechanism to meet the new conditions.

The first reaction to prolonged interference with the proper

emptying of the stomach, whether because of functional or organic disturbances, is hypertrophy of the gastric musculature. There is also a compensatory hypertrophy of the pyloric sphincter which may be mistakenly regarded as a factor in retention. Actual and progressive narrowing of the outlet, if coupled with constant overloading of the stomach with food that cannot be evacuated, will result in a gradual loss of muscular tone. The stomach becomes dilated and is sometimes capable of holding a very large amount of food without manifesting the vomiting reflex ordinarily expected.

Ptosis, of itself, does not, I believe, influence the emptying power of the stomach. The influence of the functional neuroses, general asthenias, and similar non-organic troubles on gastric motility is negligible, although on one or two occasions, by the aid of the barium motor meal, we have detected a slight six-hour retention during a severe migraine attack.

Gastric tetany, in our experience, is not a frequent or serious complication of either benign or malignant pyloric obstruction. Specific inquiry will often elicit incipient manifestations of gastric tetany, particularly affecting the extremities. Occasionally we have observed manifest gastric tetany in ulcer-bearing patients without gastric retention, either of the organic or intermittent type. Rarely a patient without organic gastric disease has a history of typical gastric tetany. It is reasonable to assume that such patients have either neurotic or spasmophilic tendencies, since evidences of these tendencies may be present in other members of the family without gastro-intestinal complaints. In the few cases of gastric tetany that we have had an opportunity to study in recent years we have consistently found a high content of non-protein nitrogen in the blood-plasma, as well as heightened carbon dioxid combining power and increased electric excitability of the nerves. These findings tend to support the observations of MacCallum and his associates, who advanced the hypothesis that the cause of tetany is due to the loss of hydrochloric acid in the gastric juice, resulting in an alkalosis. On the basis of this hypothesis they treat the complication by furnishing a large supply of chlorids. In view

of the high blood urea nitrogen, which often exceeds 100 mg. per 100 c.c. of blood, it is possible that a toxic element is a contributory or the main factor in the production of tetany (Eusterman). We are investigating this phase of the problem.

The series of cases with varying degrees of definite gastric retention which we are reporting were observed for a sufficient length of time to allow definite conclusions. Our chief object in studying these cases has been to perfect a scheme of preoperative management and observation which will bring about the greatest decrease in surgical risk with the least waste of time.

100 CASES STUDIED

From a group of 100 cases, 10 were rejected because of unsatisfactory evidence of retention. The average age of the patients was fifty-two years; 82 came to operation, with a total mortality of 13 per cent.

Gastric Carcinoma.—Twenty-nine patients had gastric carcinoma; 17 of these had partial gastrectomies; 11 had simple explorations, and 1 had a palliative gastro-enterostomy. The surgical mortality in this group was 17 per cent.

Gastric Ulcer.—In 11 cases gastric ulcer was found; two ulcers within the pyloric ring, although of questionable anatomic location, were classified as duodenal ulcer in order to avoid confusion. In only one case was there any constriction of the pyloric ring. In other words, in approximately 90 per cent. of the cases the retention was due entirely to functional disturbance of gastric motility.

Duodenal Ulcer.—In 37 cases of ulcer of the duodenum the surgeon was unable to demonstrate actual obstruction of the pylorus in 54 per cent. In 1 case only was the obstruction due to constricting bands of adhesions; in the others the narrowing was caused by callus and inflammatory swelling.

Miscellaneous.—In 1 case a foreign body was found to be partially occluding the stoma of a gastro-enterostomy performed elsewhere six months previously. In 2 cases of cholecystitis and in 1 case of appendicitis no intrinsic gastric lesions were

found to which retention could be attributed. In 1 case the only abnormality found was an obstruction by an encircling mass of adhesions.

In the cases of ulcer, vomiting, loss of weight, and irregularity of gastric distress implanted on previous characteristic ulcer histories were the most constant symptoms of retention. In the study of this group two very important facts were disclosed: first, that the surgical mortality was 16.5 per cent., and second, that 41.6 per cent. of all the ulcers were discovered at operation to be in a state of chronic perforation. That chronic gastric retention predisposes to perforation seems logical. In 1 interesting case of the series a gastric and a duodenal ulcer were discovered, both of which were perforating.

Vomiting was present in 70 per cent. of the entire series of cases. The customary type of history is that of a relatively long-standing ulcer syndrome, recently confused by a tendency to loss of weight and appetite, absence of relation to meals and food ease, persistence of trouble instead of intermittency, and, very frequently, vomiting. Emaciation and dehydration were in proportion to the degree and duration of the trouble. A definite and persisting spasm of the pylorus was reported by the surgeon in but 2 cases.

The mortality reported in this series of cases is at least indicative of the fact that whether the case is malignant or benign it offers extremely grave surgical problems and carries with it almost as great a risk as any other surgical condition.

Treatment Before Operation.—Our interest has been directed chiefly to the group of cases in which surgery has been contemplated. In cases in which gastric retention is recognized or suspected the patients are immediately placed in the hospital for observation, although they are not confined to bed unless the general condition makes it necessary. The two important factors in surgical risk are dehydration and malnutrition; the former is the more readily obviated. In the cases of marked pyloric obstruction due to malignant growths we have found that besides cleaning the stomach fairly well and partially re-

storing body fluids, nothing is accomplished by preoperative treatment, and that it is best not to hold this type of case for more than three or four days before operating. This is especially true if cachexia complicates the obstruction.

There are also certain non-malignant cases in which early operation is indicated. It is, therefore, very important to observe such patients closely during the first few days in order to judge whether or not more prolonged preoperative treatment is advisable.

Our measures of treatment have been simple. We have adhered to a liquid diet up to the time of operation, regardless of whether or not retention disappeared. The type and amount of food must depend on the possibilities of the individual case. The food should be relatively light and taken at not more than two-hour intervals. We rely largely on milk and cream, although the diet may be varied by many agreeably flavored fluids. It should be borne in mind that the importance of nourishment is secondary only to fluids, and that articles which supply both should be chosen.

Our routine procedure, so far as it may be called routine, is to wash out the stomach twice in twenty-four hours, at 11.00 A. M. and at bedtime. In mild cases once a day is sufficient as soon as the aspiration demonstrates that the stomach is recovering its tone and evacuating itself. Circumstances may make more frequent lavage advisable. On account of the increased danger of causing actual damage with the lavage tubes the work should be done by an experienced person. The lavage should be very gentle; it is better gradually to clean the stomach by repeated short lavages over a period of several days than to keep the tube in a long time at first because it is plugged by coarse remnants of food. It must be remembered that there is a tendency to malignant degeneration, to a thinning of the wall in the region of the lesion, and to chronic perforation, all three of which demand discretion in the use of the tube. The weight, color, and condition of the flesh and skin are the outward signs of reaction to treatment. Above all, the patients should be watched for signs of acute or subacute perforation.

Immediate surgery should follow the diagnosis; nothing can be gained by waiting.

From April 1, 1920 to April 1, 1921, 640 patients with duodenal ulcer were operated on at the Clinic, with a mortality of 2.96 per cent.; 47.36 per cent. of the patients who died had definite preoperative gastric retention. The surgical mortality in the entire number of ulcer cases (806) was 3.97 per cent. Fifty-three and one-tenth per cent. of the patients who died had had gastric retention, and 44 per cent., chronic or subacute perforation; 59 per cent. of the patients with retention had perforation. It may readily be seen how surgical mortality in a relatively small group of cases of gastric retention may be lost sight of in a larger series of cases of ulcer.

Close co-operation between the internist and the surgeon is imperative. We are quite convinced that we shall soon be routinely exploring and performing gastro-enterostomy under local anesthesia in this type of case, leaving more extensive work to a subsequent operation.

The necessity for a continuation of medical management for a time after operation is apparent. During this period it is advisable occasionally to test the emptying power of the stomach by tubing, and in case of motor difficulties lavage must again be resorted to.

In conclusion, it should again be emphasized that the presence of definite chronic gastric retention in a patient with a surgical lesion of the stomach immediately catalogs him as an extremely grave surgical risk; he needs all the preoperative care and treatment that it is possible for him to have expeditiously, as well as the highest available surgical skill and judgment.

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A SAFE METHOD OF REMOVING SIGMOIDAL POLYPS AND HIGH RECTAL POLYPS

LOUIS A. BUIE

POLYPS of the anorectal region are usually classified as non-malignant tumors. Before discussion of their nature is completed, however, reference is always made to their tendency to degenerate, especially the adenomatous type, which is the most usual, and when they are found, the patient is always advised to have them removed as promptly as possible. This advice is given even when the size and position of the polyps necessitate laparotomy. For these reasons it would seem justifiable to classify them as at least potentially malignant.

The method of removing polyps from the sigmoid or rectum depends on a number of factors. If the pedicle is small and it is evident that no large blood-vessels are passing through it, simple torsion, the snare, or the cautery is sufficient. If the growth is low enough, the anus can be dilated and a ligature applied before the tumor is cut away. In either case the operation can be performed without difficulty and with little danger to the patient. When the pedicle and its blood-vessels are large, however, and the tumor is so high that it cannot be drawn down far enough to permit ligating the pedicle, these methods are inadequate. It is very difficult to stop bleeding high in the rectum or above the rectosigmoid through the proctoscope. The amplitude and mobility of the bowel render effective packing impossible. There is not, apparently, any practicable manner in which a ligature can be applied through a 10-inch proctoscope, and clamps are not made for use through such an instrument which have the power to crush the vessels sufficiently to control hemorrhage. On the other hand, all clamps generally in use have the disadvantage of possessing handles that are too large to pass through the proctoscope, and it is, therefore, impossible to

remove the proctoscope without first removing the clamp. On this account it is impossible to leave a clamp attached without keeping the proctoscope in position.

Because in the Clinic a transabdominal sigmoidotomy is considered the operation of choice for a large polyp high in the rectum or in the sigmoid, and because of the risk of such a procedure, we have tried for some time to devise a means of removing these polyps through the proctoscope without the

Fig. 122.—*a*, One jaw of the clamp, which is the curved extremity of a rod. *b*, The other jaw of the clamp, which is the curved extremity of a tube. The rod extends through the tube to the thumb-piece *e*. A stationary nut, *c*, is attached to the tube. By holding *c* and turning *e* to the right, the jaw *a* is brought into contact with the jaw *b*. When the threaded nut, *d*, is screwed up by a mechanism within *c*, the force with which *a* meets *b* is increased gradually; *a* and *d* are so arranged that the wrenches, *h* and *i*, can be applied and increased pressure made without difficulty. The fork, *f*, and the hook, *g*, are to isolate and draw the pedicle of the polyp into the jaws of the clamp.

usual danger of hemorrhage. Mr. George Little, instrument maker in the Mayo Clinic, has constructed a clamp which has made this possible and which has been used successfully in three instances. The instrument, which is about 35 cm. long, is shown with the appliances used in attaching it to the pedicle of the polyp (Fig. 122).

Technic of Applying the Clamp.—The only necessary preoperative preparation of the patient is a purge and abstinence from food the evening before, and a thorough rectal irrigation

the morning of the operation. It is preferable to have the patient in bed, because he should be moved about as little as possible after the clamp is applied. With the patient in the knee-chest position the proctoscope is inserted and the polyp located. The clamp is passed in with the jaws opened as far as possible. With the fork (*f*) and the hook (*g*) the pedicle is isolated and drawn into the jaws of the clamp. After withdrawing the forks the clamp is closed on the pedicle by turning the thumb-piece (*e*) to the right; then by screwing up the threaded nut (*d*) pressure is produced that can be increased to crushing force by the wrenches (*h* and *i*), which are applied to the stationary nut (*c*) and to the threaded nut (*d*). After sufficient pressure has been made the proctoscope is withdrawn over the clamp and the patient is allowed to turn over carefully on his side. The clamp is left in position for twenty-four hours. The patient should have a sedative, and when he desires to change his position he should be assisted in order to avoid any contact that might result in pushing or pulling the handle of the clamp which projects for a number of centimeters from the anus. He should also be watched carefully during sleep.

In order to remove the clamp the wrenches are applied and the nut (*d*) is unscrewed; the thumb-piece (*e*) is turned as far as possible to the left, thus opening wide the jaws, and the clamp then withdrawn from the bowel. After this the proctoscope is inserted in order to ascertain the condition of the polyp. The patient usually remains in the hospital for two days. The polyp sloughs off within two or three days, and after a week's observation the patient is allowed to return to his home. The only disadvantage in the use of this instrument has been the fact that its handle projects from the anus, and patients must be watched very carefully during sleep; this is an insignificant objection, however, in comparison with the discomfort of the anesthesia and the risk of the other alternative, namely, laparotomy.

Mr. Little has devised an improvement on this clamp which we have not yet had the opportunity to use. The new instrument will permit leaving the clamping end, which is about 5 cm. long and smooth on all surfaces, in the bowel after the handle

has been withdrawn entirely. It is so constructed that the handle can be reapplied without difficulty. It is quite probable that this instrument will supercede the one we have been using. We have tried the principle of the spring in the Gant valve clamp, but were unable to apply it. The edges of the clamp were too sharp to be permitted to remain attached to a tumor in the mobile sigmoid, and as the high polyps are the ones with which we are concerned, the possibility of using this method was finally given up.

REPORT OF CASES

Case I (347,534). Mr. B. W. H., aged fifty-seven years, examined in the Clinic January 26, 1921, complained of bleeding. He had persistently passed fresh blood in his stools, without pain, for two and a half years. He had been treated for hemorrhoids, but the bleeding had persisted. He had had diarrhea for two weeks, and had had a resection of part of the descending colon for what was called "ulceration," two years prior to coming to the Clinic. He was in good condition after this, except that the bleeding persisted.

A polyp 3 by 3 cm. with a pedicle 2 by 1 cm. was found attached to the anterior wall of the sigmoid about 20 cm. above the internal sphincter. It was soft and eroded, and bled freely when touched. The pedicle was apparently healthy.

February 2d the clamp was applied, and removed twenty-two hours later. At the time of removal the polyp was black and reduced to about one-third its original size. During the next week the patient was examined with the proctoscope three times. February 9th, after the point of attachment of the polyp was healed, he was allowed to go home. August 18, 1921 he was examined, and no evidence of the former polyp found.

Case II (354,594). Mrs. T. B., aged sixty-five years, on examination April 6, 1921, complained of bleeding which had been constant for several years.

On proctoscopic examination a polyp 5 by 3 cm. with a pedicle 2 by 1 cm. was found on the left wall of the bowel between 15 and 20 cm. above the anus. It was degenerating and bleeding at its tip, but the pedicle was apparently healthy.

April 27th the clamp was applied, and removed twenty-four hours later. In two days the polyp had sloughed away and in a week the ulcer at the site where the pedicle was attached was healed.

Case III (361,641). Mrs. H. L. G., aged forty-five years, when she was examined June 17, 1921, complained of hemorrhoids, mucus, and blood in the stools, and difficulty in getting the bowels to move. She said that she had been losing blood constantly.

The patient's hemoglobin was only 45 per cent. On proctoscopic examination, a soft and bleeding polyp about 4 by 5 cm. was found attached to the anterior wall of the bowel near the rectosigmoid juncture; the pedicle measured about 1.5 by 2 cm.

June 25th the clamp was applied; twenty-four hours later when it was removed it seemed that the pressure had been insufficient to cause sloughing, but two days later, on examination, the entire mass had disappeared and only a small ulcer remained where the pedicle was attached. Ten days later the ulcer had healed and the patient was dismissed.

SUMMARY

1. Sigmoidal and rectal polyps, because of their potential malignancy, should be removed as early as possible.

2. There has been no safe way of removing, through the proctoscope, large polyps high in the rectum, at the rectosigmoid juncture, or in the sigmoid. The usual method of removal—laparotomy—is effective, but the attendant risk is great.

3. The removal of polyps by means of the clamp herein described is very simple; it incapacitates the patient for only a few days, and is attended with little or no risk.

I. A PRELIMINARY NOTE ON THE FOOD REQUIREMENT IN HYPERTHYROIDISM
II. A COMPARISON OF HYPERTHYROIDISM IN MEN AND IN WOMEN

WALTER M. BOOTHBY AND IRENE SANDIFORD

I

THE syndrome of hyperthyroidism, resulting from the presence in the thyroid gland of hyperfunctioning adenoma, has been clearly established by Plummer as a distinct disease. He has shown that it differs from the hyperthyroidism of exophthalmic goiter not only in the associated pathologic condition in the thyroid gland but also in the etiology, mode of onset, clinical course, physical findings, duration of symptoms, and operative results. Both diseases are characterized by an increased basal metabolic rate and the symptoms resulting from the increased rate; both may be grouped under the general term "hyperthyroidism" because in adenoma with hyperthyroidism the increased heat production is probably caused by an excess of (normal) thyroxin available to the cells of the body, while in the hyperthyroidism of exophthalmic goiter the elevated basal metabolic rate is due to an excess of thyroxin which is in some way, as suggested by Kendall, probably slightly altered in its molecular structure, thus causing the additional symptoms peculiar to exophthalmic goiter.

We have emphasized repeatedly that a knowledge of the basal metabolic rate is of great value not only because it serves as a fundamental basis for classifying disease but also because in disorders of the thyroid gland it is an index of the degree of activity of the gland. Therefore, by means of the basal metabolic rate it is possible to distinguish patients with hyperthyroidism of either type from patients with neurotic syndromes with one or more symptoms simulating those of hyperthyroidism which,

however, on analysis can be shown not to be due to an excess of the thyroid hormone.

The existence and degree of the increased heat production in hyperthyroidism is likewise of importance from a dietetic standpoint: A man aged thirty years, weighing 70 kg., and 180 cm. in height, with a basal metabolic rate of +65 per cent. will produce as his total basal calories daily 2937 calories. To the basal requirement must be added 10 per cent. for the specific dynamic action of the food ingested and 15 per cent. for the ordinary muscular movements in bed, making a total of not less than 3382 calories; if the patient is up and around his room an additional 10 per cent. for the extra work incident thereto must be added, making a total of 3560 calories daily.

Plummer and Boothby thought it possible that the total daily heat production in hyperthyroidism might be even greater than that calculated by the above method; therefore, carefully controlled dietetic experiments were undertaken, two of which are reported here in brief. As the immediate problem under investigation was to determine the total food requirement, the patients were directed to eat what they desired both in kind and quantity, and the intake and output were determined accurately and the basal metabolic rate followed daily.

The first patient, a woman aged fifty-seven years, weighing 46.7 kg., and 159 cm. in height, with an average basal metabolic rate of +40 per cent., consumed, over a period of twenty days of rest in bed, an average of 2885 calories daily. During this period of observation the patient gained 2.7 kg., but it is to be noted that she suffered from a severe cardiac decompensation so that a variable amount of edema was always present. According to DuBois' standards a normal woman of this patient's age, height, and weight produces 1210 basal calories daily, while this particular patient produced 1694 basal calories (1210 times 140 per cent.); 10 per cent. of the patient's basal heat production must be added to this figure, to allow for the specific dynamic action of the food, and 15 per cent. for slight muscular movements in bed, making the total daily requirement 2117 calories. The patient ingested 2885 calories daily, or an additional 45 per

cent. of her basal heat production, making a total intake of 70 per cent. over her basal requirement. The additional calories met the added needs of the body which were probably due, in greater part, to the patient's tremor, nervousness, and very frequent semipurposeful movements, so characteristic of hyperthyroidism, but which were in temporary suppression during the determination of the basal metabolic rate, while probably only a small proportion was stored as body tissue.

The second patient, a woman aged thirty-five years, weighing 48.3 kg., and 158 cm. in height, with an average basal metabolic rate of +50 per cent. (1920 calories daily), for a period of twenty-three days ingested an average of 3654 calories daily; the patient was in bed most of the time, but was allowed to be up and around her room for short periods during the day. She gained 0.4 kg. during the period of observation. By calculations similar to those in the first case the caloric intake needed to cover her basal heat production plus allowance for the specific dynamic action of the food (10 per cent.), for the muscular exercise in bed (15 per cent.), and for movements around the room (10 per cent.) is 2555 calories. The patient ingested 3654 calories, an addition of 55 per cent. of her basal heat production, making a total intake of 90 per cent. over her basal requirement which was needed to cover the extra requirements, such as tremor and fidgeting.

These two experiments emphasize the need of patients with hyperthyroidism for large amounts of food. Moreover, in addition to the usual allowance for the specific dynamic action of the ingested food (10 per cent.), the normal muscular movements in bed (15 per cent.), and the usual movements around the room if the patient is up and about (10 per cent.), the caloric requirement must be increased by approximately 50 per cent. of the basal heat production in order to cover the additional demands caused by the fidgeting and semipurposeful movements which are held in abeyance during the determination of the basal metabolic rate. The total food requirement, therefore, for patients with hyperthyroidism is probably rarely less and usually more than 75 per cent. above their basal heat production. The degree of this increased caloric intake is evident if the number

of calories consumed is compared with the numbers given by Magnus-Levy for man at rest and doing varying degrees of work (Table I). Unless these requirements are fully satisfied the patient will lose weight in consuming his own food stores, and not until there is an excess intake will deposit of body tissue take place. In spite of the very large caloric intake of the 2 patients cited the storage of body tissue, if any, was small, as may be seen by the slight gain in weight of both.

TABLE I

DAILY EXCHANGE FOR MAN WEIGHING 70 KILOGRAMS

(Magnus-Levy)

With hard work	3500	calories	and	over
With medium work	3100	"	"	"
With light skilled work	2600	"	"	"
With rest in room	2230	"	"	"
The minimal exchange	1625	"	"	"
The minimal exchange after food intake	1800	"	"	"
The "bed"-time (equals the average of 4 and 6)	2000	"	"	"

In addition to the high caloric requirement patients suffering from hyperthyroidism must drink quantities of fluids in order to eliminate the increased heat produced. In a normal person at rest the loss of heat is accomplished by four means: Conduction and radiation, evaporation of water from the lungs and skin, warming the food ingested, and warming the inspired air (conduction). In the patient with hyperthyroidism the large quantities of extra heat produced must be lost chiefly through evaporation of water from the lungs and skin because the possibility of an increase in the elimination of heat through the other channels is comparatively limited. In consequence, to maintain the proper water balance in the tissues and to allow for the profuse sweating and increased vaporization of water from the lungs these patients require large quantities of liquids.

With the necessity for the ingestion of such large quantities of food and liquids a great strain is thrown on the gastro-intestinal tract, and since patients with hyperthyroidism, especially, of the exophthalmic type, are prone to gastro-intestinal upsets, the diet must be carefully regulated and indigestible food avoided

to prevent, if possible, vomiting and diarrhea which, when once started, are difficult to control. It is obvious that the dietetic management is difficult because the gastro-intestinal mechanism, itself deranged by the thyroid intoxication, cannot always function properly, and of necessity the body is forced to utilize its store of food, a condition which should be avoided as much as possible.

The 2 patients cited are typical of those with hyperthyroidism; it is to be noted that they required while at rest in bed even more calories than men doing hard work, or about the same as 2 patients without hyperthyroidism. From practical experience surgeons are reluctant to operate on patients who are losing weight, and they consider those who are able to maintain weight, or especially to gain weight, much better able to withstand operation. In the hospitalization of patients preliminary to surgical procedures, therefore, care must be exercised to see that they receive sufficient nourishment, and it is important, immediately before and after operation, that these patients are not deprived of water or food for an unnecessary length of time. Hospital diets are usually planned to meet the needs of patients having either normal or decreased food requirements, and it may often be quite difficult to make interns and nurses (as well as the hospital management) appreciate the needs of patients with hyperthyroidism for large quantities of food and water. A systematic study to determine the best type of diet for patients with hyperthyroidism is being started in our laboratory. The natural desire of these patients for large quantities of food is a valuable diagnostic sign of the presence of hyperthyroidism, especially if at the same time they are losing weight.

II

The results of a series of studies published from our laboratory emphasize, as shown in Tables II and III, the points of differentiation in adenoma with hyperthyroidism and exophthalmic goiter, as first brought out by Plummer, by the difference in the age of the patient at the onset of goiter, the time elapsing between the appearance of the goiter and the onset of

the hyperthyroid symptoms, the presence or absence of exophthalmos, the blood-pressure, and the effect of operation. Since it is also of interest to determine whether any difference exists in adenoma with hyperthyroidism, and in exophthalmic goiter as it occurs in men and women, the patients have been regrouped according to sex; the results are presented in Tables IV and V.

TABLE II

STATISTICAL STUDY OF 1656 PATIENTS WITH GOITER[1]

	Exophthalmic goiter.			Adenoma.[6]	
	Two ligations, rest at home, and thyroidectomy.	One ligation and thyroidectomy.	Thyroidectomy.	With hyperthyroidism.	Without hyperthyroidism.
Patients	341	275	420	366	254
Age (years)	37	38	36	48	44
Duration of goiter (years)	3.4	3.9	5.0	18.0	15.7
Age at onset of goiter (years)	34	34	31	30	28
Duration of symptoms (years)	1.6	1.5	1.3	1.8[2]	..
Age at onset of symptoms (years)	35	37	35	46	..
Cardiac decompensation:					
Positive (per cent.)	54	48	24	46	13
Probable (per cent.)	9	5	7	10	5
Exophthalmos[3] (per cent.)	67	65	51	3[3]	2[3]
Thrills (per cent.)	63	58	39	5	4
Bruit (per cent.)	87	86	67	12	12
Weight of pathologic specimen (gm.)	59	55	51	152	187
Glycosuria (per cent.)	1.4	1	1	2	1
Blood-pressure[4]:					
Systolic (floor)	150	146	141	158	141
Diastolic (floor)	75	74	77	86	85
Pulse pressure (floor)	75	72	64	72	56
Pulse-rate (floor)	125	121	113	107	91
Basal metabolic rate (per cent.)	+65	+53	+33	+30	+2
Clinical diagnosis, correct[5] (per cent.)	99	98	97	88	98

[1] Differential diagnosis of adenoma without hyperthyroidism, adenoma with hyperthyroidism, and exophthalmic goiter. The cases of exophthalmic goiter are divided into three groups depending on the surgical treatment: (*a*) two ligations, two to three months' rest at home, and thyroidectomy, (*b*) ligation of one superior pole followed by thyroidectomy, and (*c*) primary thyroidectomy.

[2] One and eight-tenths years represents the average duration since the onset of definite symptoms; however, it is possible to elicit a history of possible duration of three and two-tenths years, and in this respect the duration differs from that of exophthalmic goiter, which has a much clearer cut onset.

[3] The exophthalmos was only slight in these cases, never graded more than 1 on a scale of 1, 2, 3, 4, and corresponded to that so frequently seen in certain types of nephritis.

[4] The "floor" blood-pressures and pulse-rates were those obtained at the time of the clinical examination with the patient sitting.

[5] The clinical diagnosis is listed as "correct" if it corresponded to the provisional report made by the examination of fresh frozen sections at the time of operation. The close agreement between the pathologist's diagnosis of adenoma, on the one hand, and diffuse parenchymatous hypertrophy (exophthalmic goiter), on the other hand, and the respective clinical diagnoses is very striking; the pathologist, however, cannot distinguish adenomas that produce hyperthyroidism from those that do not.

[6] There is an intermediate group in which pathologic examination reveals, besides the adenoma, areas of parenchymatous hypertrophy more or less typical, but isolated, not diffuse; these cases are not included in the table; they will be discussed in detail in a later paper.

TABLE III

EFFECT OF OPERATIVE TREATMENT ON 169 PATIENTS WITH EXOPHTHALMIC GOITER AND ON 115 PATIENTS WITH ADENOMA

	Exophthalmic goiter.									Adenoma			
	Two ligations, rest at home, and thyroidectomy.				One ligation and thyroidectomy.			Thyroidectomy.		With hyperthyroidism.		Without hyperthyroidism.	
	Before treatment.	Ten days after second ligation.	After two months' rest.	After thyroidectomy.	Before treatment.	Ten days after first ligation.	After thyroidectomy.	Before treatment.	After thyroidectomy.	Before treatment.	After thyroidectomy.	Before treatment.	Ater thyroidectomy.
Basal metabolic rate (per cent.)	+68	+51	+43	+20	+60	+39	+17	+36	+8	+35	+6	−3	−9
Blood-pressure:													
Systolic	139	132	131	125	137	126	119	133	122	145	133	115	115
Diastolic	75	72	72	75	71	66	71	73	73	81	78	74	70
Pulse pressure	64	60	59	50	66	60	48	60	49	64	55	41	45
Pulse-rate	122	114	108	93	116	106	92	107	86	102	79	74	73
Weight, kg	52.3	48.0	56.6	56.3	52.8	49.7	50.7	53.3	52.9				
Patients	55				42			72		92		23	

TABLE IV

1036 PATIENTS WITH EXOPHTHALMIC GOITER AND 366 PATIENTS WITH ADENOMA WITH HYPERTHYROIDISM

AVERAGES ACCORDING TO SEX

	Exophthalmic goiter.						Adenoma with hyperthyroidism.	
	Two ligations, rest at home, and thyroidectomy.		One ligation and thyroidectomy.		Thyroidectomy.			
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Age (years)	44	36	41	37	39	35	48	48
Duration of goiter (years)	1.9	3.6	2.3	4.2	5.3	4.9	13.3	18.6
Age at onset of goiter (years)	42.1	32.4	38.7	32.8	33.7	30.1	34.7	29.4
Duration of symptoms (years)	1.5	1.7	1.7	1.4	1.5	1.5	1.7	1.8
Age at onset of symptoms (years)	42.5	34.3	39.3	35.6	37.5	33.5	46.3	46.2
Cardiac decompensation:								
Positive (per cent.)	51	55	41	50	21	25	40	46
Probable (per cent.)	8	9	2	7	11	7	9	10
Exophthalmos (per cent)	57	69	63	66	52	48	0	3
Weight of pathologic specimen (gm.)	62	59	71	54	57	49	151	152
Blood-pressure:								
Systolic (floor)	142	151	144	146	141	141	155	159
Diastolic (floor)	73	75	73	75	75	78	85	86
Pulse pressure (floor)	69	76	71	71	66	63	70	73
Pulse-rate (floor)	114	126	114	123	101	115	97	108
Basal metabolic rate (per cent.)	+67	+64	63	+52	+37	+32	+32	+30
Patients	49	292	+54	212	72	348	45	321
Percentage of men and women	14	86	23	77	17	83	12	88
	Men 18 per cent; women 82 per cent.							
	Men 16 per cent; women 84 per cent.							

Percentage Incidence in Men and Women.—Fourteen hundred and two patients with hyperthyroidism were studied; 366 had adenoma with hyperthyroidism and 1036 had exophthalmic goiter; 16 per cent. of these patients are men; in other words, hyperthyroidism in this series is six times more frequent in women than in men. A slightly greater proportion of men have exophthalmic goiter (18 per cent.) than adenoma with hyperthyroidism (12 per cent.).

Age.—In adenoma with hyperthyroidism the average age for men and women is forty-eight years. In exophthalmic goiter, however, men appear for examination from four to eight years later in life than women, the average age for men being forty-one years and for women thirty-six years. The average age of all

TABLE V

RESULTS OF OPERATIVE TREATMENT ON 287 PATIENTS WITH EXOPHTHALMIC GOITER[1] AND ON 92 PATIENTS WITH ADENOMA WITH HYPERTHYROIDISM

AVERAGES ACCORDING TO SEX

	Exophthalmic goiter.												Adenoma with hyperthyroidism.			
	Two ligations, rest at home, and thyroidectomy.				One ligation and thyroidectomy.				Thyroidectomy.							
	Men.		Women.		Men.		Women.		Men.		Women.		Men.		Women.	
	Before operation.	After operation.	Before operation.	After operation.	Before operation.	After operation.	Before operation.	After operation.	Before operation.	After operation.	Before operation.	After operation.	Before operation.	After operation.	Before operation.	After operation.
Basal metabolic rate (per cent.)	+67	+19	+64	+18	+54	+19	+52	+16	+37	+10	+32	+7	+32	+5	+30	+6
Blood-pressure:																
Systolic	140	128	141	127	136	124	135	122	133	118	128	122	143	133	144	133
Diastolic	71	78	72	75	69	71	70	74	71	70	70	73	81	81	81	78
Pulse pressure	69	50	69	52	67	53	65	48	62	48	58	49	62	52	63	55
Pulse-rate	112	79	121	91	104	83	113	94	95	82	104	87	92	73	100	79
Patients	49	21	292	117	63	21	212	56	72	9	348	63	45	10	321	82

[1] Basal metabolic rate studies were not made on all patients after operation; therefore the numbers of patients before operation and after operation are not the same.

patients with exophthalmic goiter at the time of examination is thirty-seven years (Table II).

Duration of Goiter.—In cases of adenoma with hyperthyroidism the duration of the goiter in men is thirteen and three-tenths years, while in women it is eighteen and six-tenths years. In exophthalmic goiter the duration of the goiter in the three groups of men studied was one and nine-tenths, two and three-tenths, and five and three-tenths years, while in women it was three and six-tenths, four and two-tenths, and four and nine-tenths years. With the exception of the group of patients with mild exophthalmic goiter, the duration of the goiter was longer in women than in men in both diseases. It is of diagnostic significance that the average duration of goiter is markedly longer in cases of adenoma with hyperthyroidism, more than thirteen years in men and more than eighteen years in women, than in cases of exophthalmic goiter, in which none of the groups averages more than five years.

Duration of Symptoms.—The averages show a tendency toward a longer duration of symptoms in adenoma with hyperthyroidism than in exophthalmic goiter; this fact is strikingly brought out if the probable instead of the positive duration of the symptoms is taken into consideration in both diseases (Table II), because the onset is often insidious in adenoma with hyperthyroidism, while in exophthalmic goiter the onset is usually so abrupt that the date can be established readily. In general a shorter time elapses between the first appearance of the goiter and the onset of the symptoms in men than in women. In adenoma with hyperthyroidism symptoms were noticed by men eleven and six-tenths years after the onset of the goiter; by women sixteen and eight-tenths years. In exophthalmic goiter only a very short time elapsed between the appearance of the goiter and the onset of the symptoms in men, four-tenths and six-tenths years in the groups of patients with severe types of the disease, and three and eight-tenths years in a group of patients with a milder type of the disease; in women the time interval for the three groups was one and nine-tenths, two and eight-tenths, and three and four-tenths years. This slight dif-

ference in the two sexes may possibly be due to the fact that men doing heavy labor are much more quickly incapacitated for work from the hyperthyroidism than women who are doing much lighter work, and that women are more likely to recognize promptly slight alterations in the contour of the neck. From these averages (Tables II and IV) the fact is apparent that in both men and women the onset of hyperthyroidism from adenoma occurs most often after the age of forty-six, while the onset of exopthhalmic goiter is most often before the age of forty-two in men and before the age of thirty-six in women.

Cardiac Decompensation.—In both diseases cardiac decompensation is present in a greater proportion of women than of men. As would be expected, the greatest percentage occurrence of cardiac decompensation is in the severest cases of exophthalmic goiter in both men and women; the percentage occurrence then decreases with the decrease in the severity of the hyperthyroidism.

Exophthalmos.—In exophthalmic goiter exophthalmos is present in the severer cases in a larger proportion of women (69 per cent.) than of men (57 per cent.); in the mild cases the difference is not noteworthy. Moreover, the percentage occurrence decreases with the decrease in the severity of the disease. In adenoma with hyperthyroidism marked exophthalmos does not occur, no matter how intense the intoxication; occasionally a questionable or very mild degree of exophthalmos is noted in women.

Floor Blood-pressure.—In exophthalmic goiter the floor blood-pressures for both men and women decrease with decrease in the severity of the disease. It is noteworthy that in the group of severe cases while men are eight years older than women the blood-pressures are higher in the latter, probably due to the psychic reaction of the patient, since these floor blood-pressures are taken at the time of the general physical examination with the patient sitting on the table; when the patients are at rest in bed, as at the time of the basal metabolic rate determination, this difference is no longer evident, as is shown in Table V. The diastolic blood-pressure averages in the different groups studied

from 1 to 3 mm. mercury higher in women than in men. The tendency to hypertension in adenoma with hyperthyroidism and its absence in exophthalmic goiter, as pointed out by Plummer, is evident both in men and women.

Pulse-rate.—In all the groups the pulse-rate is higher in women than in men, in spite of the fact that the basal metabolic rate is higher in the latter. It is lowest in adenoma with hyperthyroidism and highest in the group of severe cases of exophthalmic goiter, decreasing with decrease in the severity of the disease. While the pulse-rate on the average parallels the basal metabolic rate, as emphasized by Sturgis and Tompkins, this does not necessarily hold true in individual patients. In order to meet the increased demand of the cells for oxygen and food in hyperthyroidism three variables come into play, one or all of which are increased: the number of heart-beats per minute, the volume output per beat, and greater utilization of the blood-carrying power. One or all three factors play a part in hyperthyroidism, and it is possible to conceive of the oxygen and food requirement being met by increased utilization of the blood-carrying power and the volume output per beat without marked change in the number of heart-beats per minute. This would explain the not infrequent occurrence of only a slightly increased pulse-rate with a moderately high basal metabolic rate. On the other hand, a patient with hyperthyroidism on admission to the hospital may have a high pulse-rate from cardiac strain with decompensation, accompanied by a moderately increased basal metabolic rate, and after three or four days' rest in bed the pulse may drop markedly and the basal metabolic rate remain unchanged. Likewise, in auricular fibrillation the rapid irregular rate does not necessarily give an index of the level of the basal metabolic rate.

Basal Metabolic Rate.—In adenoma with hyperthyroidism men tend to run a slightly higher basal metabolic rate than women. The average basal metabolic rate in each group of patients with exophthalmic goiter operated on is higher in men than in women, which, taken in conjunction with the observation that men less frequently have cardiac decompensation,

indicates that on the whole men bear the strain of the disease better than women.

Postoperative Results.—The postoperative results (Tables III and V) are comparable in men and women. There is a marked and prompt decrease as a result of surgical treatment in the basal metabolic rate, in the systolic, diastolic and pulse-pressure, and in the pulse-rate. In adenoma with hyperthyroidism the removal of the adenoma promptly cures the patient, while in exophthalmic goiter the return to normal takes place after a much longer time interval, and occasionally two or more thyroidectomies are necessary before the hyperthyroidism, especially in patients with intense intoxication, is reduced within safe limits.

SUMMARY

1. The importance of a high calory diet and large fluid intake is emphasized by two careful quantitive dietetic experiments which show that patients with a moderate degree of hyperthyroidism at rest in bed require a higher caloric intake than a man doing moderate muscular work. The total food requirement of one patient with hyperthyroidism was 70 per cent. above her basal heat production, and of that of the second 90 per cent.

2. Three hundred and sixty-six patients with adenoma with hyperthyroidism and 1036 patients with exophthalmic goiter have been studied according to sex; 16 per cent. were men and 84 per cent. women.

3. In exophthalmic goiter 18 per cent. of the patients studied are men whose average age was forty-one years, as compared with the average age of thirty-six years in women. The duration of the goiter in men in the severer cases of exophthalmic goiter is somewhat shorter than in women. In the severer cases women show a greater tendency than men to have exophthalmos; this is reversed, however, for the group of mild cases. A larger percentage of women than men suffer from cardiac decompensation. The basal metabolic rate in each group of patients operated on is somewhat higher in men than in women. Men not only have exophthalmic goiter less often but also seem to stand up

under the stress and intoxication of the disease better than women.

4. In adenoma with hyperthyroidism 12 per cent. of the patients studied are men in whom the duration of the goiter is thirteen years, compared with nineteen years in women; otherwise there is no noteworthy difference in the two sexes.

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THE DIFFERENTIAL DIAGNOSIS OF POLYURIA, WITH SPECIAL REFERENCE TO DIABETES INSIPIDUS

LEONARD G. ROWNTREE

POLYURIA is one of the three cardinal symptoms of diabetes insipidus; the others are thirst and polydipsia. In the majority of instances it is the symptom that brings the patient to the physician. Since it is a common finding in certain other diseases differing widely in prognosis and treatment, and since the diagnosis of diabetes insipidus is often one of exclusion, differential diagnosis in patients with polyuria becomes a matter of great importance, and often is of considerable difficulty.

DIABETES INSIPIDUS

For the past two years diabetes insipidus has greatly interested me and two of my associates, Dr. Larson and Dr. Weir. During this time we have had the opportunity of observing 16 cases and have carried on investigations in this disease and in polyuria in other diseases, especially with regard to the effect of various therapeutic procedures.

The term "diabetes," derived from the Greek, signifies "siphon," and was first used by Aretæus, the Cappadocian. Diabetes insipidus was described by Frank in 1794 as "a long-continued abnormally increased secretion of non-saccharine urine which is not caused by a disease condition of the kidneys." Since no better definition has been suggested, this is usually accepted.

The disease is rare. Eichhorst found only 17 cases in 35,492 patients in the medical clinic at Zürich between 1876 and 1877; Gerhardt, 55 in 113,600 patients treated at the Charité, Berlin, from 1877 to 1896, and Futcher, 7 in 403,535 patients treated in the Johns Hopkins Hospital and Dispensary from 1889 to 1904.

A study of the records of the Mayo Clinic reveals 34 cases in 370,000 patients. Thus, in a total of more than 800,000 patients there are only 113 cases of diabetes insipidus.

The history of diabetes insipidus dates back to Willis, who, in 1874, differentiated by the taste of the urine saccharine and non-saccharine forms of diabetes. Scattered reports of instances of diabetes insipidus are found in the literature subsequent to Frank, but no definite progress was made until the beginning of this century. It was regarded as an interesting disease of metabolism of unknown etiology. The frequency of nervous symptoms caused it to be considered a manifestation of a functional neurosis. Tallqvist and Meyer revived some interest in it a decade or two ago, suggesting that it was due to the inability on the part of the kidneys to secrete a concentrated urine. As a result of the work of Schäfer and his colleagues, which called attention to the influence of the extract of the posterior lobe of the hypophysis on the urinary output, a new interest has been created in the subject. Although their work led to erroneous conclusions, it centered the attention of the medical world on the subject, with the result that in 1913 von den Velden, in Germany, and Farini and Ceccaroni, in Italy, working independently, administered pituitary extract to patients suffering from diabetes insipidus. This treatment controls all its cardinal symptoms for temporary periods at least.

Experimentally the disease has been produced through removal of the posterior lobe of the hypophysis and by section of the infundibulum, but the results have been lacking in uniformity. Bailey and Bremer have obtained polyuria with great constancy through lesions involving the tuber cinereum.

The patient before us, Miss L. K. (Case 556,430), is one of the most interesting in the series studied. She is thirty-four years of age, a stenographer by occupation. Her father and mother are living and well, 1 brother and 4 sisters are living; 2 of the latter have valvular heart lesions, and 2 are subject to sick headaches; 1 brother died at birth and 2 sisters in infancy. The family history is negative for tuberculosis, carcinoma, renal disease, diabetes mellitus, and diabetes insipidus. Menstrua-

tion, which began at twelve, is regular every twenty-four days, lasts for from five to seven days, and, except that it is slightly excessive at times, it is normal. The patient had measles, mumps, and chicken-pox during childhood, and an attack of influenza in 1918.

The patient's chief complaints are increased thirst, polyuria, polydipsia, fatigue on slight exertion, sleepiness, and "stomach trouble." These symptoms began in March, 1911, when the patient was doing much extra work and was somewhat worried. One afternoon she was suddenly seized with extreme thirst and drank a large amount of water, more than 9 liters. Later she developed polyuria and passed large quantities of pale urine. She believes that the thirst preceded the polyuria; however, on close questioning, she is not absolutely certain that this was the case. Her mother ascribes the disease to a spell of hysteria, at the age of fifteen, following an attack by a dog, and claims that the patient has been nervous since that time. However, nine years intervened before the onset of diabetes insipidus. Thirst, polyuria, and polydipsia have continued since 1911, and she still drinks large amounts of water (9 to 12 liters daily) and passes approximately the same amount of urine. This is not associated with polyphagia; in fact, thirst destroys her appetite, and she says that she cannot eat when she is thirsty. With the onset of her trouble she lost 20 pounds in weight, and during the first two years suffered much from headaches, which have since disappeared. However, prior to the onset of this condition she had sick headaches.

The patient also has some digestive disturbances, but no evidence of any organic disease, such as ulcer. The gastric discomfort is partially relieved by soda. At times she complains of weakness of the back, and at other times of persistent sleepiness.

Physical examination reveals a rather thin and nervous woman weighing approximately 100 pounds. The positive findings, which are few, consist of dry skin, a systolic murmur at the apex of the heart which is not transmitted to the axilla, a liver edge palpable just below the right costal margin, a palpable right kidney which is not unduly movable or tender, and slight

obscuration of the upper and temporal margins of the disk in the right eye. The blood-pressure is 116 systolic and 84 diastolic.

The urine is large in quantity, varying from 8 to 12 liters a day, with a specific gravity of from 1.001 to 1.005, and neutral or acid in reaction. It contains occasional traces of albumin, but no sugar; the sediment shows an occasional pus-cell. Under the influence of pituitrin the urine dropped to from 2 to 3 liters a day, with a specific gravity as high as 1.019. Additional chlorids were excreted, with an increase in polyuria and a salt output somewhat in excess of the intake. Renal function is normal; the phenolsulphonephthalein return is 55 per cent.; uric acid is 1.9 mg., creatinin 1.5 mg., and urea 21 mg. per 100 c.c. of blood. Plasma chlorids vary from 0.575 to 0.597 per cent. The blood contains 77 per cent. hemoglobin, 4,840,000 red cells, and 8200 white cells. The Wassermann test on the blood is negative.

x-Ray examination of the teeth shows one root and two teeth to be extracted. The *x*-ray of the sella turcica is negative. The visual fields are normal.

COMMENT

This is an instance of primary diabetes insipidus, primary because no cause has been found. The group of idiopathic cases embraces all those associated with marked functional or neurotic syndromes solely, those of an hereditary nature, and those which are temporary, as in pregnancy. In the group of secondary cases are included those with organic lesions of the nervous system, tumors of the hypophysis with characteristic syndromes, such as *typus Fröhlich* or infantilism, with or without neighborhood manifestations, cerebral neoplasms, and injuries to the head, particularly fractures of the base of the skull and cases of general disease capable of causing lesions in the brain, through metastasis from carcinoma or sarcoma, or through inflammatory deposits or subsequent atrophy, syphilis, tuberculosis, actinomycosis, and lethargic encephalitis. Inasmuch as this patient believes that the thirst and polydipsia preceded the polyuria, this may be an instance of primary polydipsia in the sense of Ebstein.

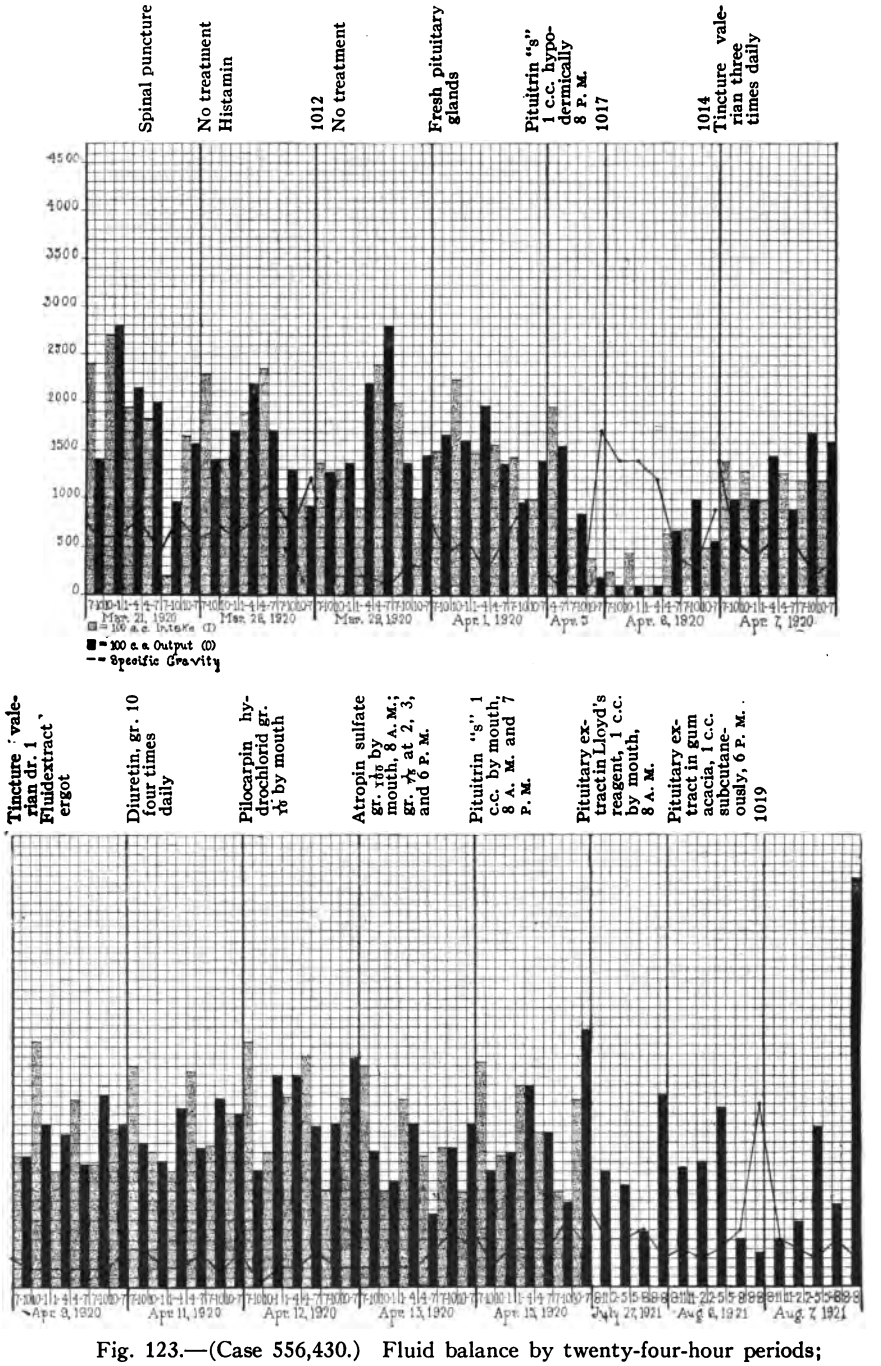
Spinal puncture
No treatment Histamin
1012 No treatment
Fresh pituitary glands
Pituitrin "s" 1 c.c. hypodermically 8 P. M. 1017
1014 Tincture valerian three times daily
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Mar. 21, 1920
Mar. 26, 1920
Mar. 29, 1920
Apr. 1, 1920
Apr. 5
Apr. 6, 1920
Apr. 7, 1920
= 100 c. c. Intake (I)
= 100 c. c. Output (O)
= Specific Gravity
Tincture valerian dr. 1 Fluidextract ergot
Diuretin, gr. 10 four times daily
Pilocarpin hydrochlorid gr. 1/6 by mouth
Atropin sulfate gr. 1/60 by mouth, 8 A. M.; gr. 1/75 at 2, 3, and 6 P. M.
Pituitrin "s" 1 c.c. by mouth, 8 A. M. and 7 P. M.
Pituitary extract in Lloyd's reagent, 1 c.c. by mouth, 8 A. M.
Pituitary extract in gum acacia, 1 c.c. subcutaneously, 6 P. M. 1019
Apr. 9, 1920
Apr. 11, 1920
Apr. 12, 1920
Apr. 13, 1920
Apr. 15, 1920
July 27, 1921
Aug. 6, 1921
Aug. 7, 1921

Fig. 123.—(Case 556,430.) Fluid balance by twenty-four-hour periods; collections at three-hour intervals during the day, twice during the night. The intake was not recorded the last three days.

Symptomatically the case is of moderate severity. The fluid intake and the urinary output have exceeded 12 liters a day at times. This appears moderate in contrast with Trousseau's case, in which the urinary output reached as high as 43 liters a day and the water intake 40 liters. However, a water balance of 12 liters a day is sufficient to cause great inconvenience and to disturb the patient frequently during the night, and the thirst occasions great discomfort. It is interesting that, aside from headache, there is in this patient no evidence of cerebral involvement, such as increased intercerebral pressure, focal or general signs of brain tumor, and that *hemianopsia bitemporalis fugax,* which occurs frequently in diabetes insipidus secondary to basilar meningitis, is conspicuously absent.

This young woman has been the subject of many therapeutic experiments and has entered heartily into the spirit of our investigations. The various forms of treatment utilized and the results obtained may be seen in Fig. 123. Pituitary extract, 1 c.c. of the extract of the posterior lobe administered subcutaneously, has been effectual, as a rule, over periods of about twenty-four hours. Throughout the last one and a half years she has depended on it entirely, having had on an average four injections a week. The pituitary extract has proved a great source of comfort to her.

Among other therapeutic measures she has had a spinal puncture, has been fed the fresh gland (posterior lobe up to eighteen fresh glands a day), and has been given histamin, valerian, ergot, diuretin, pilocarpin, and atropin, all of which have failed utterly with respect to the symptoms and the course of the disease. Special preparations of pituitary extract with Lloyd's reagent and salol-coated pills have also failed. Subcutaneous administration of pituitary extract suspended in gum acacia resulted in complete control of the symptoms, but the local irritation was somewhat greater than that associated with the use of the ordinary extracts on the market, and the period of control was not increased.

DIFFERENTIATION OF VARIOUS FORMS OF POLYURIA

In the differentiation of the various forms of polyuria consideration must be included of physiologic polyuria, diabetes mellitus, chronic interstitial nephritis, polycystic disease of the kidneys, infection of the kidney or of the urinary tract, and functional nervous disorders.

Physiologic polyuria is extremely common and occurs after the ingestion of large quantities of fluids, and frequently also under extreme nervous strain and excitement. Its temporary character readily differentiates it from the polyuria of diabetes insipidus and other diseases in which the increased urinary output is persistent over long periods.

Diabetes Mellitus.—The diagnosis of diabetes mellitus, as a rule, is made readily. The symptoms accompanying its onset are often characteristic, and include polyphagia, thirst, polydipsia, polyuria, and loss of weight and strength. The urine, as a rule, is large in amount, of high specific gravity, and contains sugar and often acetone and diacetic acid. The level of the blood-sugar is usually increased and the tolerance for glucose diminished. In addition, proper dietary control in the majority of cases results in the prompt disappearance of the glycosuria and of the hyperglycemia and its associated symptoms.

Sugar appears in the urine occasionally in diabetes insipidus, and cases are recorded in which diabetes mellitus has terminated eventually in diabetes insipidus. In this connection the level of the blood-sugar may be of the greatest significance, especially in cases complicated by nephritis. In one such case that has come to my notice a high threshold for sugar was responsible for the disappearance of the glycosuria. As a result of the nephritis the threshold for sugar was raised to such an extent that the glycosuria disappeared despite the presence of marked hyperglycemia. Conversely, it is claimed that diabetes insipidus sometimes terminates in diabetes mellitus. Senator reports an interesting case of a woman forty-three years of age, who, from childhood, had passed from 10 to 12 liters of urine daily. She developed a persistent glycosuria three years before death. At necropsy no etiologic factor was discovered. Such cases are infre-

quent. Only in the rarest instances is difficulty encountered in differentiating these two forms of diabetes. No difficulty has arisen in any of the cases in our series.

Chronic Interstitial Nephritis.—The chief source of error in diagnosis is found in chronic interstitial nephritis, in which polyuria is of frequent occurrence. If outspoken clinical manifestations are present, chronic nephritis is readily diagnosed. On the other hand, its pathognomonic signs and symptoms may be lacking, especially in children, under which condition its existence can be determined only by renal functional studies. The truth of this was revealed to me in a most striking manner by the case of a boy, aged twelve years, who was admitted to the wards of the Johns Hopkins Hospital with what was considered an interesting case of diabetes insipidus. His past history contained nothing of importance, except that he had passed excessive quantities of urine for some time and had experienced marked thirst. On admission the urine varied from 2000 to 2500 c.c. daily, was clear, with a specific gravity of from 1.005 to 1.010, and was free from albumin and casts. Physical examination revealed nothing of importance. A phenolsulphonephthalein test revealed marked renal insufficiency, on the basis of which the diagnosis of chronic interstitial nephritis was made. A week later headache developed and a trace of albumin appeared in the urine. The patient rapidly became uremic and died. Necropsy revealed advanced chronic interstitial nephritis. Other somewhat similar cases have since been encountered and a group of such cases in children has been reported recently by Taylor. Since albumin occurs in many cases of diabetes insipidus and since in chronic nephritis the absence of albuminuria may persist over long periods, studies of the urine alone do not suffice.

Renal functional studies should be made in all cases in order to differentiate diabetes insipidus and chronic interstitial nephritis. In this connection we have attempted to determine the presence or absence of organic or functional disturbances in the urinary tract in this series of cases of diabetes insipidus. Careful studies of renal function have failed to incriminate any part of the alimentary tract as an etiologic factor, and little or no de-

viation from normal function has been discovered except in relation to excretion of water and perhaps of salt. The excretion of phenolsulphonephthalein and the values for blood urea, creatinin, and uric acid were uniformly normal. Cystoscopic examination in 2 cases revealed normal bladders. Ureteral catheterization revealed the fact that the increased secretion of urine was bilateral, and approximately proportional for both kidneys, and that the appearance of phenolsulphonephthalein was normal from each side. Administration of the pituitary extract with the ureteral catheters in place, reaching to the pelvis of the kidney, resulted in the control of the polyuria and in a change in the concentration and color of the urine, within eight minutes in one case, and within ten minutes in another. In chronic interstitial nephritis, on the other hand, marked reduction of the renal function is the rule. The phenolsulphonephthalein excretion is decreased, while the blood evidences increase in the urea, creatinin, and uric acid. These functional evidences of renal insufficiency are frequently present in chronic interstitial nephritis in the absence of all clinical signs and symptoms of uremia. Attempts to control the urinary output by the use of pituitary extract have failed in our cases.

Polycystic Disease of the Kidneys.—Polyuria is a frequent accompaniment of polycystic kidneys. The urinary findings are difficult to differentiate from those of chronic interstitial nephritis. Physical examination in the later stages at least, as a rule, reveals vascular and cardiac changes similar to those encountered in chronic interstitial nephritis, and, in addition, palpable masses in the loins. The condition is one which is frequently missed during life and often encountered unexpectedly at necropsy It should always be kept in mind, and palpable tumors in the loins should be sought before a diagnosis of diabetes insipidus is made.

Infection of the Kidneys or of the Urinary Tract.—In many instances infection in the urinary tract is associated with polyuria and pollakiuria. As a rule, however, some discomfort is experienced in voiding, and urinalysis indicates infection somewhere in the urinary tract, albumin, pus, and sometimes red blood-cells being present. The polyuria, as a rule, is not so excessive as in

diabetes insipidus, and thirst does not play a very prominent part. The difficulty in the differentiation is illustrated by the following case:

Mr. T. B. (Case 316,215), who is forty-six years of age, is a stationary engineer. His family history is negative except for the fact that his father died of paralysis at the age of fifty-two. He has been married two years and has 2 children. Twenty-five years ago he contracted a neisserian infection, eighteen years ago he had pneumonia, and six years later erysipelas.

The patient's chief complaint is frequency of urination and pain in the back. Three years ago he began to void every half-hour during the day. There was no pain, burning, or loss of blood. He voided two or three times during the night. His condition gradually has grown worse. When he works he drinks excessive amounts of water and passes much urine. One year ago he was told that the prostate was enlarged; he was treated for five months without improvement. A second physician also diagnosed enlarged prostate and treated him for three months without improvement. A third physician diagnosed diabetes insipidus. Aside from frequency of voiding and weakness in the back the patient felt well. Insidiously the condition became aggravated. Slight smarting and difficulty in starting the stream were experienced at times. The patient passed 4 liters of urine in twenty-four hours and was up three to five times at night. He lost from 18 to 20 pounds and constipation became marked. Periods of sexual weakness were noted from time to time.

The patient is small and thin. The positive findings include dental sepsis Grade 3, prostate size Grade 2, and tonsils size Grade 1, on a basis of 1, 2, 3, 4. On ophthalmic examination floating vitreous opacities were found. The pupils, fundi, and visual fields are normal. The nasal septum is deflected. Blood-pressure is 130 systolic and 80 diastolic.

The urine varies between 3 and 5 liters a day. Albumin is constantly present in traces; the specific gravity at times reaches as high as 1.010 and a few pus-cells are constantly present. The phenolsulphonephthalein output is 50 per cent. and the blood urea 18 mg. per 100 c.c. The blood shows hemoglobin 74 per

cent.; the red cells number 4,500,000, and the white blood-cells 15,800; the Wassermann test on the blood is negative.

x-Ray examinations of the sella turcica, chest, kidneys, ureters, and bladder were negative. The neurologic examination was negative.

This patient has been under observation and treatment for a number of weeks. Early in his examination Dr. Braasch and his associates did not believe that there was sufficient evidence to incriminate the urinary tract. Careful studies in the medical ward convinced us that the patient did not have diabetes insipidus. Rest exercised considerable influence in decreasing the urinary output. Thirst was never a matter of great importance clinically. Pituitary extract had no effect in controlling the polyuria or the frequency of urination, and the constant presence of traces of albumin and a few pus-cells pointed to disease of the urinary tract. The patient was returned to the Section on Urology, where a diagnosis of chronic prostatitis and seminal vesiculitis was made, and local applications administered. On cystoscopic examination local areas of cystitis were found, which were treated by injection of argyrol. Only after ureteral catheterization and culture of the urine obtained directly from both kidneys the condition was diagnosed bilateral pyelonephritis.

The uncertainties in this case illustrate remarkably well the difficulty of diagnosis in a considerable number of cases.

Functional Nervous Disorders.—Hysteria often occasions great difficulty, and only in the presence of stigmata or other prominent hysteric manifestations the nature of the polyuria becomes apparent. On the other hand, hysteria itself is frequently difficult to recognize, its diagnosis also often being made only by exclusion. Unquestionably, in the past many patients with early cerebral lesions have been classified as hysteric. True diabetes insipidus may occur in association with hysteria, or possibly at times it may be hysteric in origin. It is frequently associated with marked neurosis, which is at times primary and at others secondary. In one of our cases the greatest difficulty was encountered in determining the nature of the polyuria:

Mrs. L. A. (Case 323,015) was twenty-eight years of age

on examination July 5, 1920. Menstruation had begun at sixteen years and had always been irregular, lasting for from five to six days, with loss of a normal amount of blood. She had been married for six years, had had 2 children and no miscarriages.

The patient became unconscious at the age of two following a bite on the right eyelid by a dog, and at the age of twelve following a fall on the ice. Two years before examination she had again been rendered unconscious by a blow over the right eye. She had had headaches from the age of eight to twelve, and stated that during this time she had suffered from numbness throughout her left side. This, however, had entirely disappeared at the time of examination except from the fingers and hands, which were still numb at times. She stated that her legs had been paralyzed for three weeks during her last pregnancy. During both pregnancies she had been somnambulistic, and on one occasion in her sleep had walked the top of a high fence. Her husband had found it necessary to lock her in her room to prevent her wandering away in her sleep. She had had scarlet fever as a child, influenza in 1918, and pleurisy in 1919. Attacks of tonsillitis had been frequent.

During the six weeks before examination the patient had suffered much from thirst and had passed excessive quantities of urine. During this period her skin had been unduly dry. These symptoms may have lasted longer; of this the patient was uncertain. Ten years before she had been caught in a cyclone and since had been very nervous. She claimed to have had an electric shock at the time. As a result she is filled with terror during every thunder storm. She had felt weak for two years and had been much worried for the last six weeks. Fainting had been frequent since the age of twelve and she had had attacks of dizziness from time to time. She complained that for many years she had been the victim of a dual personality, "Jane the worker," and "Janette who loves to play," who she felt had quite distinct personalities. However, Dr. Woltman, who studied the case carefully, did not believe that she had a true dual personality. He made a diagnosis of psychoneurosis, petit mal, and migraine.

Physical examination revealed an undernourished, slender, apathetic woman of about thirty years of age. The only positive findings were a scar on the right lower eyelid, five teeth with periapical infection, a somewhat enlarged heart with a systolic murmur at the apex which was not transmitted to the axilla, tenderness over McBurney's point and along the course of the aorta, a polar right kidney, slightly palpable inguinal and cervical glands, and at times inequality of the knee-jerks.

The urine varied from 4 to 6 liters a day, of specific gravity of 1.007 to 1.009; it was acid in reaction and occasionally contained traces of albumin and a few pus-cells. Renal function was normal, with 55 per cent. return of phenolsulphonephthalein. The blood showed 78 per cent. hemoglobin, 4,700,000 red cells, and 7000 white cells. The Wassermann reaction on the blood was negative.

The *x*-ray examination of the sella turcica showed it to be normal. An electrocardiogram recorded a sinus bradycardia.

The gravest difficulty was encountered in attempting to interpret the polyuria in this case. The patient was extremely psychoneurotic. The polyuria was of short duration and moderate in degree. She was worried about her condition and extremely anxious to get well. Pituitary extract administered subcutaneously controlled the polyuria promptly, and for a period of two or three days. Voluntary control was attempted in this case because the patient believed that she could control her thirst "by sheer will power." In order to augment the will power the water was cut off from her room and a limit of 2 liters placed on her intake. Although she suffered greatly from thirst, she succeeded in persisting in the plan for five days, and reduced the intake to 2 liters a day and the output to approximately the same amount, the specific gravity rising proportionately.

Our diagnosis was diabetes insipidus, psychoneurotic or hysteric in origin. The clinical picture is in striking contrast in many respects to the majority of cases of diabetes insipidus which have come under our observation. It also emphasizes the difficulties incident to the differentiation of some forms of polyuria and to the recognition of diabetes insipidus.

In a second case of polyuria of neurotic origin (Case 353,026) the patient was assured that she did not have diabetes insipidus which had been diagnosed by her local physician. Since returning home the polyuria has ceased entirely and the patient has gained 30 pounds in weight.

Of 36 cases tentatively diagnosed diabetes insipidus in the Mayo Clinic prior to 1920 only 24 appear to be true instances of the disease. In cases incorrectly diagnosed the urinary tract is most frequently the seat of pathology. As time passes experimental studies are yielding a clearer conception of the nature of diabetes insipidus which counts for greater accuracy in diagnosis. Experimental methods have already produced in the extract of the posterior lobe a remedy potent symptomatically.

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TYPES OF DIABETES MELLITUS

RUSSELL M. WILDER

MY purpose this afternoon is to speak about the existence of separable types of diabetes mellitus, a subject which attracted my interest several years ago and which deserves, I believe, more discussion than it has received.

For some time after Bright's discovery that the urine of the nephritic patient contained albumin, all the albuminurias were considered one clinical entity, namely, Bright's disease. Similarly, today diabetes mellitus is diagnosed whenever a persistent glycosuria is encountered, and in most clinics is assumed to be a clinical entity. Is such an assumption justified?

In diseases of the kidney advances have been made; the various types of nephritic disorders are being sharply differentiated, and the term "albuminuria" is recognized as meaning any one of a variety of definite and distinct pathologic conditions. Is it possible to do likewise for the glycosurias? A diagnosis of diabetes mellitus is limited by von Noorden and most clinicians to the cases of glycosuria in which there is a continuous excretion of sugar with the patient on a general diet. The occasional and transitory glycosuria which follows the ingestion of a single large dose of glucose, and the glycosuria which is provoked by injections of adrenalin, or by injuries to the brain, are not classed as diabetes. Moreover, the occasional case of glycosuria in which the blood-sugar is normal has been set apart as the so-called "renal diabetes." There remain, however, a number of clinical syndromes which are quite distinct except for the common symptom of glucose in the urine, and while various types of diabetes are recognized by experienced clinicians, few attempts have been made to classify them critically. For the most part patients with diabetes are grouped according to age or according

to the degree of severity of the disease, a differentiation which does not recognize the possibility of dissimilarity in the diabetes.

There are a number of reasons to account for hesitancy in grouping diabetic patients more critically. First, pathologists and surgeons have helped us less in diabetes than in almost any other field of medicine. Such information as necropsy and biopsy have afforded has tended to complicate the situation more than to clarify it. Despite the brilliant studies of Opie, Weichselbaum, and Hansemann, no consistency whatever has been found, save in individual instances, between the severity of the pancreatic lesions and that of the diabetes. Indeed, in the severest forms of the disease the pancreas may appear entirely normal, or show at most such granular changes in the islet or acinous cells as occur in other cachectic conditions (Fahr, Major, Seyfarth). Second, we have as yet no laboratory criterion that is helpful in determining the type of the disease. Sugar may be very abundant in the urine and the blood-sugar may be very high both in the acute form of diabetes and in the relatively milder conditions. The same is true of acidosis and blood fats. Joslin has warned against the possible confusion of severe acidosis in diabetes and severe diabetes. Finally, it is probable that overlapping occurs between different types of the disease, and that even if we should ultimately obtain positive diagnostic criteria enabling us to divide the glycosurias into three or four fairly distinct clinical entities, a percentage of our cases would fall into more than one group. This is true of the nephropathies, and there is every reason to believe that it is also true of the group of syndromes which we now speak of collectively as "diabetes mellitus." In spite of these many difficulties, however, certain very definite clinical features permit a grouping of cases, and while we undoubtedly are in danger of error in attempting such grouping in the absence of pathologic confirmation, a certain definite advantage is to be gained by doing so.

TYPES OF DIABETES MELLITUS

Since January, 1920, we have been diagnosing the type of the disease, grouping our cases as follows:

Group 1. Acute diabetes, characterized especially by abrupt onset and gradually falling carbohydrate tolerance, strength, and weight.

Group 2. Vascular diabetes associated with hypertension or arteriosclerosis, or both, with or without renal complications.

Group 3. Diabetes of obesity, characterized by obesity, without evidence of vascular disease.

Group 4. Interstitial pancreatitis.

Group 5. Miscellaneous persistent glycosurias.

Recently Brigham published an analysis of the 600 cases of diabetes treated in the last six years at the Massachusetts General Hospital, comparing them with an equal number of cases observed there during the preceding ninety years. A classification is adopted with which our observations are in very fair agreement. By far the smaller number of cases in his series are the so-called "true diabetics" (our Group 1), represented by the child, the young adult, the thin middle-aged person, or even the person in early old age. His second group comprises those patients with low carbohydrate tolerance without true diabetic symptoms, but in whose urine sugar is found in large amount in the course of routine examination, for instance, the candy factory girl. (We have not been able to recognize this type with certainty.) His third group are the obese patients whose ages are between thirty and fifty years who do well if treated intelligently. A small fourth group includes patients who are pregnant, or those who have thyroid or other endocrine disturbances. A fifth group of patients, 2 or 3 per cent., give positive Wassermann reactions and are usually not so sick as one would expect; they improve rapidly with proper treatment for syphilis. A sixth group, the largest (our Group 2), is represented by the patients with arteriosclerosis and those with impairment of the kidney, or circulatory disturbances. In the seventh group are described those healthy appearing persons who have considerable sugar in the urine and a moderate amount of sugar in the blood, but without symptoms or loss of weight.

Our series includes 298 patients with diabetes mellitus observed in the Mayo Clinic between January 1, 1920 and January

1, 1921. Recent data have been obtained from 194 of these. About one-third of them (100 patients) were held for a time in the hospital receiving careful instruction in dietetics and in the use of food tables, so that they could continue careful dieting at home.

GROUP I: ACUTE DIABETES

Fifty-seven of these 298 patients, 19 per cent., were placed in Group 1. These are the so-called true diabetics; we have called them acute diabetics rather than true diabetics, since some of the patients in the other groups have very severe forms of the disease and would certainly be called true diabetics by those who use the term in this limited sense. The criteria for the group are abrupt onset, steadily falling carbohydrate tolerance, and loss of weight. The experienced physician recognizes these patients at a glance. They present themselves for treatment early in the course of their disease. A definite date can usually be established on which excessive thirst and polyuria commenced. Acidosis[1] often appears very early and may become extreme and cause death within a few weeks. Loss of weight and strength date from the onset and continue rapidly until dietary control is instituted. Then follows a more chronic period with more or less subsidence of the cardinal symptoms, depending on the adequacy of the management, but with the tolerance for carbohydrate falling rapidly in some cases, more slowly in others, but steadily in all. Proper treatment delays this course, but does not check it completely, and death is usually ushered in by coma.

For the most part the patients of this group were young; 7 of our series were children, and the average age was twenty years. Age, however, is not an absolute criterion. Fifteen of our patients were more than forty years and five were more than fifty. Thirty-nine of the series were females and 18 were males.

[1] The term "acidosis" is used in this paper in the sense intended by Naunyn, to indicate an increased production of acids. Acidosis may or may not be accompanied by a measurable diminution of the alkali reserve, depending on whether or not sufficient alkali is being supplied to make good the alkali deficit (Woodyatt, R. T.: Acidosis. Nelson Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1920, iii, p. 8).

The data are insufficient to establish a racial influence. Heredity for diabetes was less frequently observed than in other groups. It could be traced in 15 instances. Heredity for obesity was present in only 5. Only 3 of the patients were overweight before the onset of the disease.

The etiology of this form of diabetes is obscure. A story of dietary excess before onset or of overeating of sweets was obtained in only 10 cases. Physical exhaustion may have played a part in 4 cases and nervous exhaustion, worry, or anxiety in 4. In only 2 instances was there any suggestion of abdominal pain which may have been a pancreatitis; 15 cases followed rather shortly after attacks of influenza, which may or may not have done more than to precipitate a potential diabetes about to break out spontaneously. In 22 cases there had not been evidence of any serious infection antedating the onset of diabetes. The latter burst out of a clear sky as it were. In several of these patients the urine had been examined within a year previous to the onset and had been reported negative for sugar.

GROUP 2: VASCULAR DIABETES

Eighty-nine patients, 30 per cent. of the entire series, showed hypertension or palpable arteriosclerosis, and were, therefore, given a diagnosis of vascular diabetes. This form of the disease is strikingly different from that of patients in Group 1. The onset is insidious in almost every case; the patient seeks medical advice not because of loss of weight or of thirst, or polyuria, but because of some complication such as gangrene or angina pectoris; in some cases the sugar was discovered accidentally in the course of a routine physical examination. With the exception of one man of thirty-one years all the patients in the group were more than forty years of age; 57 were males and 32 were females.

The diabetes in Group 2 is milder than in Group 1. Acidosis is less frequently encountered, and occurs later in the course of the disease; often some infection is found to account for it in part. Loss of weight is less. Although some of these persons ultimately become very thin, they rarely show a definite cachexia. A rather large percentage of the group tend to obesity. The

concentration of sugar in the urine may be quite high, 6 per cent., but polyuria is infrequent. The blood-sugar is usually high, from 0.3 to 0.5 per cent., and often is depressed with difficulty, even by fasting. The course of the disease is chronic. One of our patients had survived for twenty-seven years, despite very inadequate dietary control. Not infrequently a tendency to recovery from the diabetes is observed. A few of the patients in this group did not, even on general diets, show sugar in the urine when seen recently, although previously they had excreted large amounts. The sugar in the blood of these patients remained high, even after the discontinuance of the glycosuria. While the underlying diabetes in these cases is mild, the so-called classical complication of diabetes occurred in patients of this group with much greater frequency than in the other patients. All the cases of diabetic retinitis observed during the year gave definite evidence of vascular disease (Wagener and Wilder). Gangrene occurred exclusively in this group. Cataract or lens opacities were found in 22 patients of this group and in only 6 of all the other group combined. Psychosis, neuritis, and paresthesias have been more frequent in this group. It would appear that several of these conditions, instead of being complications of diabetes, should be regarded as of vascular origin.

The etiology of this type of diabetes is not definitely settled, although it is highly probable that the diabetes itself is due to arteriosclerosis. There is very little evidence in any of the patients of this series to show that diabetes preceded the vascular disease. The reverse is the case. A family history for heredity for diabetes occurred in 18 cases.

GROUP 3: DIABETES OF OBESITY

In Group 3 of the series were 45 cases, 15 per cent. These include the majority of our obese patients, but not all of them, since those with vascular disease were arbitrarily added to Group 1 and a number were added to Group 4. There remained 45 overweight persons with presumably normal vascular systems and normal kidneys, without evidence of abdominal disease.

Heredity for obesity was present in 16 of these and heredity for diabetes in 11. Race may be a factor; 50 per cent. of our Jewish patients belonged to the group; 22 were males and 23 females; 7 patients were between the ages of thirty-one and forty years, 14 were between forty-one and fifty years, and 16 were between fifty-seven and sixty years.

The diabetes tends to be mild. The onset, however, may be fairly acute, and is thus recorded in 5 cases. Pruritus is a common complication and is often the presenting symptom at the first medical examination. Peripheral pains are met with frequently. Cataract was observed only once. The course of the disease is chronic; one patient in the group had had sugar in the urine for eighteen years. Glycosuria is readily controlled even by qualitative reduction of the carbohydrate quota of the diet and the tolerance for carbohydrate falls very slowly, if at all, provided adequate dietary management is instituted. On the other hand, in the absence of management the cardinal symptoms of diabetes may become as prominent as we find them in patients with acute diabetes, so that an error in diagnosis or, rather, an incorrect interpretation of the underlying diabetes, is easily made. In one patient a daily excretion of 5000 c.c. of urine was observed, in another a sugar concentration of 8 per cent. was recorded, and the maximum sugar excretion for twenty-four hours was 315 gm. The sugar in the blood may be just as high in this group, or higher, than in patients in Group 1, and acidosis may be quite as intense. It has been our experience, in fact, that patients of this type are rather sensitive to acidosis. Fasting, which throws them on their endogenous metabolism, may be equivalent to forcing them on a very high fat diet and seems to be particularly dangerous in this type of case. Woodyatt, writing on acidosis in 1916, refers to a certain proportionality which probably must exist between the rates of combustion of fat and carbohydrate. The patient with diabetes, owing to his diminished rate of sugar oxidation, can thoroughly oxidize less fats than the normal person, and, therefore, keto-acids accumulate. Fasting will lower acidosis either in health or in diabetes if it has the effect of stopping a one-sided metabolism and throwing the tissues on

a more nearly balanced ration of fatty acids and glucose; the effect would be the reverse if the imbalance were increased.

GROUP 4: INTERSTITIAL PANCREATITIS

In Group 4 were 53 patients who had interstitial pancreatitis, either proved by exploratory operation or suggested strongly by the presence of cholecystitis or other inflammatory condition near the pancreas. Many of these patients were operated on at the Clinic because of gall-bladder disease or other abdominal disorders, and in some of them we were able to obtain specimens of pancreatic tissue for microscopic examination.

The patients of this group are often obese, and in general the clinical picture of the diabetes is not unlike that of the diabetes of obesity. The course of the disease is chronic; 15 patients had had glycosuria of known duration for more than six years, and one for more than twenty-five years. The type of onset was gradual in 33, acute in 8, and questionable in 12. There was a definite history of increase in weight preceding the onset in 13. The cardinal symptoms of diabetes may be absent entirely or they may be very pronounced, as in the preceding group. The striking feature is the relative ease with which the disease may be controlled by dietary measures.

GROUP 5: MISCELLANEOUS PERSISTENT GLYCOSURIAS

Besides the four main groups the series contained a scattering of relatively fewer cases, as follows: Five patients had tumors of or involving the pancreas; 15 patients had glycosuria following hyperthyroidism; 5 patients had tumor of the brain, with glycosuria, which was apparently of central nervous origin. Only 1 patient had syphilis antedating the onset of the diabetes. He improved remarkably on treatment for syphilis. In 4 patients the criteria of so-called renal diabetes were fulfilled; the remaining 24 were not classified. These latter represented in part persistent glycosuria without other clinical manifestations. Most of them were middle-aged persons. Two were young. Whether they will later develop frank diabetes remains to be seen.

I regret that I cannot speak with certainty concerning the prognosis in each of these several groups. Another five years must elapse before this can be determined, but from the returns received thus far it would appear that very few, if any, of the patients with acute diabetes will survive more than two or three years. On the other hand, it is probable that the patients with vascular disease (Group 2), the obese patients (Group 3), and those with interstitial pancreatitis (Group 4) will show very favorable survival percentages at the end of five years.

In the group of 57 patients with acute diabetes 43 have been traced successfully; 14 have died, most of them in coma, within an average of less than two years from the onset of their trouble. Thirty-nine of the 57 patients were educated in dietetic methods of control and were discharged from the Clinic on diets which maintained them free from sugar and acidosis.

In the group of 89 patients with vascular disease, of which 57 have been traced, 10 have died. Many of these deaths are due to complications attendant on hypertension, nephritis, and arteriosclerosis; if the age of these patients is taken into account, it will be seen that the mortality is relatively low compared with that in patients with acute diabetes.

Of the 45 obese patients of whom 31 were traced, only 2 deaths have been reported, and in the 51 patients with presumptive evidence of interstitial pancreatitis, 39 of which have been traced, there have been only 5 deaths.

Since diabetic patients usually die after they leave the hospital and go home, it will always be difficult to obtain necropsy data. Only 8 of the entire series were lost while under our care. Four of these died following major operations; 2 were not operated on, but died in coma within twenty-four hours after they arrived at the Clinic; both had the acute type of the disease. One patient had severe empyema and high-grade pancreatitis and one had exophthalmic goiter. The latter case is of sufficient interest to warrant a brief consideration:

Case 149,225. Mrs. M. R., aged forty years, first came to the Clinic in January, 1916. She complained of leukorrhea and pruritus, the former having existed for several years; the latter

was of recent onset. At intervals during the past two years she had drunk considerable water. She felt thirsty at night and urinated six times during the day and two or three times at night. Her mother had died of blood-poisoning and was thought to have had diabetes; a brother had had diabetes for four years, and one sister who died later of the influenza was said to have had "a touch of diabetes." The patient was 5 feet, 9 inches tall and weighed 165 pounds. Four years before she is said to have weighed 210 pounds. Other members of the family were not obese.

Examination revealed a well-nourished woman. Her systolic blood-pressure was 142, and her diastolic 86. The blood count was normal. The urine contained 10 per cent. sugar in one specimen, and 7.8 per cent. of 3550 c.c., or 277 gm., in twenty-four hours. Acetone and diacetic acid tests were negative. A blood-sugar determination made four hours after an ordinary meal was recorded as 0.744 per cent. At that time attempts were not being made in the Clinic to treat diabetes and the patient was referred to Dr. Hodgson of Waukeshaw, who placed her on a diet and taught her to examine her urine. For the following three years she kept herself free from sugar and from all diabetic symptoms on food which she made no attempt to weigh, but which was merely a qualitative restriction of carbohydrates and consisted of vegetables, fruits, meat, fish, eggs, and "hepco" bread. In December, 1919 a goiter was noticed, and she became nervous, lost in weight and strength, perspired freely, and developed a ravenous appetite. Unable to restrain her appetite, she broke her diet and ate liberally of carbohydrates. Sugar reappeared in the urine and an excessive thirst developed.

In September, 1920 the patient returned to the Clinic with severe exophthalmic goiter. She weighed 112 pounds. The systolic blood-pressure was 164 and the diastolic was 76. The basal metabolic rate was +91 per cent. The heart was enlarged and in auricular fibrillation and markedly decompenstaed. The patient's legs were edematous.

Examination revealed a movable mass in the right upper quadrant which was diagnosed distended gall-bladder. On inquiry it was learned that the patient had been aware of this for

the past sixteen years. At no time, however, had she had symptoms of gall-bladder disease. Examination of the urine revealed 4 per cent. of 2500 c.c., or 100 gm. of sugar, in twenty-four hours. Acetone and diacetic acid tests were negative. Rest in bed and the usual medical measures for hyperthyroidism were adopted. No attempt was made to restrict the diet, except that sugar and sweets were omitted from the food. The goiter symptoms increased in severity. October 10th the basal metabolic rate was +101 per cent. Finally with myocardial failure an extreme anasarca developed and the patient died October 28th. The sugar in the urine had not at any time exceeded 115 gm. in twenty-four hours. The sugar in the blood on the day before the patient died was 0.25 and the alkali reserve on this day was 50 per cent. with the acetone in the urine limited to a trace.

Necropsy revealed hypertrophy of the thyroid, general anasarca, cardiac hypertrophy, chronic cholecystitis with cholelithiasis, perihepatitis, chronic pancreatitis, and bilateral cloudy swelling of the kidneys. Histologic examination showed hypertrophic and hyperplastic thyroid with lymphocytic infiltration and chronic interstitial pancreatitis.

The case is of interest from many angles, but is cited here chiefly to illustrate certain points which I have emphasized. Diabetes presumably began at least two years before January, 1916, when the patient was first seen in the Clinic. During these two years she had not been sick enough to consult a physician. She had lost in weight, but was still well nourished and did not complain of loss of strength. After a diet was instituted sugar disappeared from the urine, and for four years she experienced no difficulty in avoiding glycosuria or loss of weight, even with a diet in which only a qualitative restriction of carbohydrates was attempted. The development of exophthalmic goiter should undoubtedly be regarded as purely accidental. Had this not occurred there is no reason to believe that she would not have been living today, with glycosuria still under control. This is not an instance of the group of cases of hyperthyroidism and secondary glycosuria, but rather of a true diabetes complicated in its course by exophthalmic goiter.

The sequence of events leading to the development of diabetes was cleared up by finding a definite pancreatitis at necropsy. A symptomatic cholecystitis had existed for years, in the course of which the interstitial pancreatitis occurred, in all probability secondary to the infection of the gall-bladder. The case belongs, therefore, in Group 4, and, had the type of the disease been recognized in 1916, an error in prognosis might have been avoided. A very bad prognosis was given at that time because of the high blood-sugar and the large amount of urinary glucose, but this was not justified. In view of the insidious onset, the relatively tardy development of severe symptoms, and the evidence of coexisting cholecystitis the subsequent chronic course could have been anticipated.

COMMENT

A differentiation of these several types of diabetes is of real importance and not merely a matter of academic interest. The prognosis in a given case, as I have illustrated, depends more on the nature of the underlying diabetes than on the temporary severity of cardinal symptoms or the intensity of the glycosuria. The same is true of the surgical risk of any given case. Berkman reported recently a large series of operations on diabetic patients in this Clinic. A remarkably low mortality occurred as compared with Foster's series, for instance, but a comparison of the two reports is not justifiable because we saw no data in either of these reports concerning the type of case in which operation was performed, and it is highly probable that the series that contained the largest number of cases of acute diabetes would show the higher mortality, other factors being equal. Likewise for accurate comparison of various therapeutic procedures we must have information as to the type of the disease. The average length of life of Joslin's patients treated by the Allen method is seven years. Newburgh and Marsh recently have reported favorably on the benefit of higher calory diets. It would help us to gage the relative merit of the two procedures if more specific data were at hand on the number of patients of each group contained in each series.

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THE RELATION OF FOCAL INFECTION TO DISEASES OF THE URINARY TRACT

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THE oral sepsis so frequently present in patients with various forms of kidney and bladder infections, and the various hypotheses with regard to the pathway by which infections reach the urinary tract, have suggested the possibility that such sepsis is a focus for bacteria having a selective affinity for the urinary tract.

The proximity of the kidneys to the colon and what appears to be direct lymphatic connection between them has led many research workers and clinicians to believe that the lymphatics are the pathway of renal infections. Colon bacilli in most specimens of infected urine have supported this belief.

All observers seem to agree that infection may and frequently does reach the urinary tract through the blood-stream. The presence of typhoid bacilli in the urine of patients with typhoid fever is common knowledge. Brown demonstrated that the urine of patients having pulmonary tuberculosis contained acid-fast bacilli, although at necropsy the kidneys did not show lesions.

Because of the absence of colon bacilli from dental and tonsillar sepsis the idea that such sepsis could be the cause of urinary infections has seemed improbable. That the organisms which reach the kidney and produce lesions later resulting in a colon bacilluria may be other than colon bacilli was suggested by LeFur. He attempted to produce vesical ulceration in laboratory animals by the intravenous injection of various bacteria. The results were so unsatisfactory that the intravenous injection was abandoned and the organism was injected directly into the bladder or into the perivesical space. Ten different strains of bacteria, including the streptococcus, the pneumo-

coccus, and the colon bacillus, were used. When the colon bacillus was injected it was recovered in pure culture; when other organisms were injected the colon bacillus was often recovered with the injected organism. In 3 cases the colon bacillus alone was recovered, even though a different organism had been injected in pure culture. This evidence is certainly suggestive that the colon bacillus may be a secondary invader, and, considered with the well-known fact that any disturbance in the urinary tract, such as the presence of stone, stricture, or prostatic obstruction, is generally followed by a colon bacillus infection, makes the possibility of its playing a similar secondary part in most urinary infections seem credible. With this idea in mind Dr. Meisser and I some time ago selected patients with non-specific urinary infections in whom possible foci were demonstrable and obtained cultures from both the extracted teeth and tonsils. From the former we always obtained green-producing streptococci, while from the latter more varied flora were obtained which, however, always included green-producing streptococci. Samples of these cultures were injected intravenously into laboratory animals. We have recently reported a series of experiments in which of 92 rabbits thus injected 72 developed lesions of the urinary tract. During this study we discovered that following the eradication of the patients' suspected foci the urinary symptoms were greatly aggravated, and a severe reaction often occurred, during which bacteria identical to those obtained from the teeth or tonsils were recoverable from the urine, although only colon bacilli had been found. These streptococci obtained in mixed cultures with colon bacilli were also injected intravenously into rabbits and displayed a selective affinity for the urinary tract similar to that displayed by the bacteria from the teeth and tonsils. In one patient a positive blood-culture was obtained during the reaction following the extraction of her teeth, and from this streptococci were isolated which produced lesions of the kidney when injected into laboratory animals.

These results led us to believe that urinary infections may often be due to focal infections harboring streptococci which have a selective affinity for the urinary tract, and that the colon

bacillus, which is commonly found and generally believed to be the cause, is of secondary importance.

I shall report in this paper the clinical results obtained by the application of these experimental findings. In our search for foci of infection roentgenograms were made of the teeth to demonstrate the presence or absence of apical abscesses and devitalized teeth, and the teeth were all carefully examined by means of the pulp tester in order to ascertain their viability. The pulp tester was used because in making routine cultures of extracted teeth we have found that pure cultures of green-producing streptococci may be isolated at the apices of dead teeth, even if the roentgenograms do not reveal evidence of periapical infection. It is not generally appreciated that there may be a vast number of organisms around devitalized teeth before sufficient bone is destroyed to make their presence manifest in the roentgenograms. I believe, therefore, that it is a mistake to exclude the teeth as a possible focus of infection simply because apical abscesses are not demonstrable by the *x*-ray. The same may be said of the tonsils. The fact that they are not enlarged and that pus cannot be expressed from them does not exclude them as possible foci. It is our custom to recommend tonsillectomy in all cases in which the urinary infection may be reasonably believed to be of focal origin. Since the procedure has been adopted a surprisingly large number of apparently negative tonsils has been found to hide deep-seated virulent infections. The failure to appreciate that devitalized but otherwise negative teeth and innocent-appearing tonsils may act as foci of infection undoubtedly explains the many failures to obtain favorable results after the partial removal of such foci.

RESULTS

Reports have been received from 64 patients treated in the clinic during 1920 for non-specific urinary infections. The majority of these patients had pyelonephritis, some had simple ulcers of the bladder, others had submucous ulcers, and a few had idiopathic cystitis. Twenty-five (39 per cent.) of the 64 patients gave histories of previous tonsillitis, and 18 of pus

expressed from the tonsillar crypts, thus a total of 43 patients had evidence of tonsillar infection; 45 of the patients had one or more abscessed teeth, revealed by the Roentgen ray. This incidence of infection is much higher than the average, and hence seems significant. Forty-five of the patients had possible foci removed either at the Clinic or after leaving; of these, 10 had tonsils alone removed, 28 teeth alone, and 7 both teeth and tonsils; 35 patients report definite improvement and alleviation of symptoms, in as striking contrast to that formerly obtained when only local treatments were given as the letters expressing satisfaction are in contrast to former communications of discouragement and discontent. It must be borne in mind, however, that the results obtained by the removal of foci of infection from patients suffering from urinary infections will be in direct ratio to the duration of the disease, for a kidney badly damaged by long-continued infection is no more able to resume complete function than is an arthritic joint in which bony changes have occurred, simply because the original focus in the tonsils or teeth has been removed. The secondary colon infection may have resulted in even greater damage to the urinary tissue than the original streptococcal infection, and it is most important to realize that our well-established methods of combating such infections by means of lavage should not be abandoned. Such treatments are often of the greatest benefit in correcting the damage, and if undertaken only after all possible foci are removed will be of far more lasting benefit than in the past. I believe that our experimental work, with the clinical diagnoses, demonstrates a close relationship between oral sepsis and urinary infections.

THE TREATMENT OF DYSMENORRHEA

LEDA J. STACY AND EDWARD G. JOSEPH

DYSMENORRHEA may be divided clinically into two types: In cases of the first type examination discloses definite pathologic conditions, such as fixed retroversion, chronic pelvic infection, acute anteflexion with marked retrocession, uterine myomas, a long conical cervix, and a pin-point os. In the second type there is no demonstrable pathology. The uterus is freely movable, and normal in position and size. The external os is not contracted. The great bulk of dysmenorrheas (93 per cent. in our series) are classified as the second type; they are further subdivided into two groups, obstructive dysmenorrhea and congestive dysmenorrhea.

1. **Obstructive Dysmenorrhea.**—In these cases pain precedes the onset of the flow by several hours or even by several days, and is relieved when the flow becomes well established. Many theories have been advanced to account for this syndrome. Theilhaber attributes the pain to the spastic contraction of the circular muscle-fibers around the internal os in women possessing an abnormal nervous irritability. Menge refers the trouble to the physiologic menstrual contraction waves of the uterus which are felt as labor-pains by hypersensitive women. Both theories are sustained by the facts that while these pains are present the flow is scant or even has not begun, and that the pains may be relieved by an antispasmodic, such as atropin. This is manifested clinically inasmuch that when the flow becomes profuse the pain is less.

2. **Congestive Dysmenorrhea.**—The pain in these cases occurs simultaneously with the flow and is believed to be due to hypofunction of the ovaries with deficiency of the ovarian or the lutein extract. In some of the cases in this group there is a

history of rapid increase in weight and marked diminution in menstrual discharge; in others the flow is not diminished and there is no sudden increase in weight, the so-called neuralgic form of dysmenorrhea in poorly developed, constipated, and asthenic girls.

Numerous methods of treatment of dysmenorrhea, both medicinal and surgical, have been advocated, with indifferent results in many instances. Small doses of thyroid extract, ovarian and lutein extract, and benzyl benzoate have been given. Macht demonstrated that the pharmacologic and therapeutic action of papaverin owes its inhibitory and tonus lowering properties to the benzyl component of its molecules. He accordingly searched for a simple non-alkaloidal and non-narcotic compound containing the benzyl radical which could be administered to animals without toxic results. He was eminently successful in his search, for he was able to demonstrate that benzyl benzoate (the benzyl alcoholic ester of benzoic acid) fulfilled these conditions. The drug is obtained by the fractional distillation of the oily liquid which is separated by agitating balsam of Peru with sodium hydroxid, $C_7H_5O_2C_7H_7$. Its action is identical with that of papaverin; it inhibits peristalsis of the rhythmic contraction of the smooth muscle-fibers, lowers their tonicity, and relaxes the spasm. Litzenberg in 1919 reported a series of cases in which the patients were treated successfully by a 20 per cent. emulsion of benzyl benzoate in mucilage of acacia flavored with aromatic elixir of eriodictyon. Since Litzenberg's report his preparation has been used at the Clinic in a series of cases of dysmenorrhea of the obstructive type. The dosage is from 1 to 2 drams given at the onset of the pain and repeated if necessary in from one to two hours. If relief is not obtained with the two doses, relief is not to be expected by continuation of the treatment.

The dysmenorrhea tablets used in the Clinic contain

Arsenious acid	gr. $\frac{1}{60}$;
Strychnin sulfate	gr. $\frac{1}{60}$;
Extract thyroid, siccus	gr. j;
Calcii glycerophosphate	gr. iij;
Blaud's mass	gr. iij.

The principal operative procedures have been dilatation and curetment, Alexander's external and internal operation, Pozzi's operation, and dilatation and curetment with the insertion of Baldwin's tube.

RESULTS OF OPERATIVE AND MEDICINAL TREATMENT IN 541 CASES

A series of 541 cases of dysmenorrhea in the Clinic from 1917 to 1920 inclusive have been reviewed. Of this number, 342 patients have been traced. A comparison has been made between the medicinal and the surgical treatments and between the relative therapeutic values of the various drugs.

In 71 cases in which dilatation and curetage had been performed, 20 patients (28.16 per cent.) were permanently relieved. In 45 cases of dilatation and curetment with insertion of Baldwin's tube 6 patients (13.33 per cent.) were relieved. In 24 cases of dilatation, curetage, and Pozzi's operation 5 patients (20.83 per cent.) were relieved. In 24 cases of dilatation, curetage, and Alexander's operation 8 patients (33.33 per cent.) were relieved. The statistics for the group in which the Baldwin's tube was used are probably not so favorable as they should be, for in some cases the tube was removed within three weeks after the operation.

In the group in which only medicinal treatment had been given the results were more successful: 36 (57.57 per cent.) of a group of 66 patients to whom benzyl benzoate was given were relieved; 11 (52.38 per cent.) of 21 patients given corpus luteum extract were relieved; 6 (37.50 per cent.) of 16 patients given ovarian extract were relieved; 5 (45.45 per cent.) of 11 patients given thyroid extract were relieved; 9 (36 per cent.) of 25 patients given dysmenorrhea tablets were relieved.

It may be objected that benzyl benzoate does not cure the condition, but merely alleviates the pain. This certainly is true, but it must be borne in mind that the drug is used only one day in every month and that it has no toxic or narcotic properties.

In our series of 541 cases 118 married women were operated on for sterility and dysmenorrhea; 81 replied to the subsequent

questionnaire, and 23 (28 per cent.) had become pregnant; 82 of the 111 unmarried women have been heard from, and 15 (18 per cent.) only reported relief following operation.

These data demonstrate that since a 57 per cent. relief may be obtained with benzyl benzoate and a 52 per cent. relief with corpus luteum, as contrasted with only an 18 per cent. relief with dilatation and curetage in the unmarried patients, it would be more satisfactory to give these two drugs and general hygienic measures a thorough trial before resorting to the discomforts and uncertainty of surgical procedures. With few exceptions, surgery should be limited to those cases of dysmenorrhea which are associated with sterility or some definite pathologic condition.

Until very recently the habits and general physical condition of the patient have received little attention as etiologic factors. Many such patients are constipated, have poor posture, are shallow breathers, and are of the general asthenic type. The institution of definite general physical exercises, abdominal breathing, and relief of constipation may accomplish as much or more than the treatment by drugs and surgery.

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CLINIC OF DR. JOHN H. STOKES

Five Cases Illustrating the Non-specific Effects of Treatment with Arsphenamin and the Principles Underlying the Therapeutic Test for Syphilis.

Five Cases Illustrating Aspects of the Treatment of Syphilis of the Cardiovascular System.

Three Cases Illustrating the Confusion of Gumma with Other Pathologic Processes.

Possible Erroneous Interpretations of the Tonsillar Chancre and the Cervical Satellite Bubo.

The Control of Exfoliative Dermatitis Following Administration of Arsphenamin.

THERAPEUTIC tests are so frequently used in the diagnosis of syphilis that I should like to present to you 5 cases illustrating aspects of this procedure which are apt to be overlooked in routine application. In conjunction with this group of cases is a summary of the principles underlying the use in diagnosis of the therapeutic test for syphilis.

Case 308,385 is that of a woman with lymphocytic infiltration of the skin of the face shown in Fig. 124. Clinically the infiltration involved the subcutaneous tissues, imparting to them a dusky, almost cyanotic lividity. The infiltrate was firm, not attached to the bone, and never ulcerated. This lesion by histologic examination was shown to belong to the group of sarcoids and to conform in particular to the type of the subcutaneous sarcoid of Darier-Roussy. Sarcoids in general are lymphomatous infiltrations in the skin, some of which have a granulomatous architecture suggesting tuberculous etiology. This is especially true of the sarcoids of Boeck and Darier-Roussy. In this patient no clinical evidence of tuberculosis could be found and a careful

Fig. 124.—(Case 308,385.) Sarcoid infiltration of the face of the subcutaneous or Darier-Roussy type.

Fig. 125.—(Case 308,385.) Effect of twelve arsphenamin injections on the Darier-Roussy sarcoid shown in Fig. 124. Note the large amount neces sary to produce this result.

search for syphilis was entirely negative except for the presence, on two occasions seven months apart, of partial positive Wassermann reactions (seven negatives intervening). A partial positive Wassermann reaction cannot be unqualifiedly accepted as proving the syphilitic character of lesions with the characteristics of sarcoid. It has been pointed out, however, that lesions of a sarcoid type may appear in patients who have syphilis as well as in patients who do not. Sarcoids even in the demonstrable ab-

Fig. 126.—(Case 308,385.) Effect of eighteen arsphenamin injections on the sarcoid shown in Fig. 124.

sence of syphilis are known to respond both to the administration of arsenic and of arsphenamin. Figures 125 and 126 represent the response of this patient to three courses of arsphenamin treatment administered during a period of thirteen months. In all probability the effect is non-specific. The involution of the lesion was much slower than one would expect of a syphilid under similar circumstances. Arsphenamin, accordingly, cannot be used to differentiate lesions of this type from syphilids by therapeutic test.

Case 314,465 presents further evidence that arsphenamin has marked effects on non-syphilitic lesions and is, therefore, unreliable for therapeutic tests.

This patient, shown in Fig. 127, exhibits the highly characteristic eruption of severe acnitis. Acnitis of Barthelmey is the papulonecrotic tuberculid of the face. A search for a focus of tuberculosis failed to reveal anything conclusive. He gave, however, a history of empyema with roentgenographic evidence

Fig. 127.—(Case 314,465.) Severe papulonecrotic tuberculid of the face (acnitis).

of peribronchial infiltration and old pleurisy at the right base. Diminished resonance and breath sounds were noted below the seventh right interspace. No evidence of concomitant syphilis could be elicited. The eruption had been present for ten weeks. During this time the patient had been given mercury by mouth by his physician to the point of salivation, without effect. Figure 128 shows the prompt response to seven injections of arsphenamin, 3 to 4 dg. each at weekly intervals. While the

Fig. 128.—(Case 314,465.) Effect of seven arsphenamin injections (0.3 to 0.4 gm.) on the tuberculid (acnitis) shown in Fig. 127.

Fig. 129.—(Case 217,180.) Sporotrichosis of the thigh (cultural identification) healed by arsphenamin and mercury succinimid without iodids or *x*-ray.

patient has had occasional lesions since, he has remained comparatively free for seventeen months. This might be regarded as a positive therapeutic test for syphilis were it not well established that tuberculids respond to arsphenamin, when vigorously used, with almost the completeness of syphilids. The ready response to arsphenamin, with resistance to mercury, is quite characteristic. A physician who begins his treatment for a

Fig. 130.—(Case 307,538.) Nodose erythema (erythema induratum?) of the leg before arsphenamin treatment.

supposed syphilid with arsphenamin may secure a seeming confirmation of the mistaken belief that his patient has syphilis.

Case 217,180 illustrates a lesion which gave a false therapeutic test for syphilis (Fig. 129). The lesion is a superficial, somewhat irregular ulcer on the outer side of the thigh with an arc of six nodular lesions extending upward, suggesting in configuration a nodulo-ulcerative syphilid. While the Wassermann

reaction was negative on several occasions, tissue removed from the lesion showed a granuloma with vascular changes suggesting syphilis. The patient was placed on intravenous arsphenamin injections, and the intramuscular administration of mercury succinimid as a therapeutic test for syphilis. The lesion healed

Fig. 131.—(Case 308,538.) Nodose erythema shown in Fig. 130 after one course of six and two courses of three intravenous injections of arsphenamin.

completely in six weeks. Just at this time the bacteriologic laboratory reported the rather slow-growing cultures obtained from the lesion which showed the ulcer and the associated nodules to be sporotrichosis. No iodid or *x*-ray had been used in accomplishing the cure.

Case 307,538 illustrates the lesions of a nodose erythema of a

type approximating the erythema induratum of Bazin. These lesions are somewhat atypical in that they have not undergone definite ulceration. The erythema induratum of Bazin is a tuberculosis of the skin which responds to the administration of arsphenamin. One course of six and two courses of three arsphenamin injections yielded the result shown in Figs. 130 and 131. Practically all the nodose lesions and the dusky tumid infiltration of the skin of the leg had disappeared. The patient occasionally has small nodules which are palpable, but not visible, and which disappear spontaneously. No definite focus of tuberculosis could be found and syphilis could be quite definitely excluded. Arsphenamin cannot be used in therapeutic tests to distinguish such lesions from syphilis. The occasional occurrence of partial positive Wassermann reactions in processes of this type which form the cutaneous expressions of a combination of tuberculous infection with focal septic infection has led to more than one false diagnosis of syphilis.

Case 203,812 presents an unusual variation in the non-specific therapeutic test for syphilis with arsphenamin.

Stricture of the Rectum with History of Syphilis Misdiagnosed Syphilitic Stricture. Improvement Under Arsphenamin (False Therapeutic Test). Subsequent Discovery of Amebic Infection. Second Penile Lesion with Rupia. Reinfection, Superinfection, or Monorecidive with Complete Relapse (?).

Case 203,812, Man aged twenty-eight years, single.

8/4/17 Examined.
History of Penile Lesions 1914. Lesions healed by one large dose of arsphenamin on seventh day. Four scars present. Partner known to have had active syphilis.
Duration of Symptoms: Six years.
Symptoms: Pain in the rectum and at the umbilicus.
Physical Findings: Penile scars.
Proctoscopy: Rectal stricture 10 cm. from anus. No ulceration.
Diagnosis: Probable syphilitic stricture.
Serum Wassermann Reaction Negative.
Stool Examination Not Made.
Therapeutic Test: Six arsphenamin injections, twenty inunctions.
Marked Improvement: Blood and pus disappeared. Diagnosis regarded as established.
Operative Dilatation: Stricture found to be a thin diaphragm, not an annular or funicular infiltration.
4/12/18 Re-examined: Diagnosis of alveolar abscess, chronic constipation, neurosis.
6/5/18 Relapse with blood and pus in stool.
Relief complete following six more arsphenamin injections.
11/18/19 First Stool Examination: *Endameba histolytica found.* Previous relief evidently due to effect of arsphenamin on this condition. Ipecac now gave prompt relief. *Treatment for syphilis stopped.*
12/2/19 Fainted on Street: Cause not ascertained. Stools negative.
4/1/20 Re-entered Clinic with Violent Headaches, worse at night, duration six weeks.
History of Penile Lesion which had involuted two weeks before entry; marked adenitis.
Symptoms and Signs:
Weight loss 30 pounds.
Rupial lesions on trunk and extremities; about a dozen appeared four weeks after penile lesion, one week after headaches.
Profuse sweating.
General adenitis.
Arthritis, left shoulder-joint.
Serum Wassermann Reaction Negative.
Neurologic Examination: Negative. No signs of brain gumma.
Bárány test positive with reduced bone conduction.
Treatment:
Mercury Preparation.—Ten injections mercury succinimid intramuscularly.
Arsphenamin.—Six injections of from 2 to 4 dg. at weekly intervals.
Rapid improvement under mercury and later under arsphenamin. Weight gain 20 pounds. Rupia disappeared. Bárány test revealed marked improvement.
6/10/20 Returned for Second Course after forty inunctions.
All Symptoms Disappeared, weight gain 30 pounds.
Did not report for third course.

Discussion

1. **The disparity between the duration of symptoms (six years) and the duration of infection (three years) was overlooked** at the outset and led to a hasty diagnosis of syphilis. Such time relations are highly significant.

2. **The history of the original syphilitic infection seems reasonably trustworthy.** The disease was probably aborted by the one arsphenamin injection on the seventh day, or suppressed so that superinfection or complete recurrence was possible.

3. **The rectal stricture, possibly secondary to an old amebic ulceration, was misinterpreted** as of syphilitic origin on account of the marked relief of symptoms resulting from the effect of arsphenamin on the amebic colitis.

4. **The deceptive possibilities of the non-specific action of arsphenamin** (a false therapeutic test) are apparent.

5. **Although the second penile lesion was healed** before the patient appeared with his second syphilitic infection, the rupia, constitutional symptoms, Bárány findings, and therapeutic response make it seem highly probable that the patient had sustained a reinfection or a superinfection.

6. **Malignant rupial syphilis is occasionally Wassermann negative.** The patient has never had a positive Wassermann reaction on the blood under our observation, although apparently he has been through two syphilitic infections.

PRINCIPLES UNDERLYING THE THERAPEUTIC TEST FOR SYPHILIS

1. **Do not perform therapeutic tests** for a vague and indefinite group of symptoms, such as loss of weight, malaise, headache, and so forth. The results are not trustworthy.

2. **Do not make a therapeutic test on a genital lesion.** Prove or disprove syphilis by the dark field, by Wassermann follow-up, by complete examination, and by observation.

3. **Do not invite deceptive non-specific responses** by using iodids on any lesion, or arsphenamin on patients with lesions when you wish to differentiate tuberculosis from syphilis.

4. **Therapeutic tests for tuberculous processes should be made with mercury** (the bichlorid or succinimid intramuscularly) and arsphenamin later.

5. **A therapeutic test implies observation during the test.** It is at its best on visible lesions, and its value is proportional to the definiteness and measurability of the symptoms and signs, and of the improvement which takes place in them.

6. **In late visceral syphilis,** especially cardiovascular lesions, symptomatic improvement may establish the diagnosis in spite of the fact that no change may occur in the structural signs.

7. **Spontaneous improvement in some conditions** may produce the impression of a positive therapeutic test; that is, in multiple sclerosis and some heart conditions.

8. **Therapeutic tests for syphilis must not be obscured** by the simultaneous use of other forms of treatment, such as the *x*-ray to a mass of glands or other lesions, the removal of focal infections, local applications and rest, salicylates in joint involvements, and so forth.

9. **Mixed treatment by mouth has no place** among therapeutic tests for syphilis.

10. **Not less than forty inunctions** are necessary to a therapeutic test.

11. **Intramuscular injections of a soluble mercurial salt may be used** (bichlorid or succinimid daily for from two to three weeks) for rapid effect if there are no contraindications.

12. **Not less than four arsphenamin injections** should be used in a therapeutic test which is to depend on symptomatic improvement for a positive decision. An exception is gastric syphilis, in which the symptomatic response is usually immediate.

13. **Do a provocative series of Wassermann tests** after the first injection of an arsphenamin therapeutic test.

14. **If the question of operable malignancy versus syphilis is raised,** operability has the right of way (except for a single sterilizing dose of arsphenamin), and the patient should be explored before a therapeutic test is considered. This is also true in an undoubtedly syphilitic patient if the question is raised as to whether a visceral picture is due to operable malignancy or to syphilis. If the condition is inoperable, treatment for syphilis takes first place.

15. **In a cutaneous non-ulcerative lesion** with a negative Wassermann reaction two arsphenamin injections at the most should produce practically complete involution (ten to fourteen days). If more injections are needed the test is indeterminate. Extensive ulcerative lesions may require special judgment.

16. **A local flare-up, the so-called Herxheimer reaction,** occurs immediately following the first arsphenamin injection with many visible lesions, and should be watched for. Insist on daily observation the first week and even hourly observation the first twenty-four hours.

17. **A symptomatic constitutional flare-up may also occur.** Both may be delayed in bone cases.

18. **As examination for evidence of syphilis becomes more complete and critical** there is less and less need for uncontrolled therapeutic tests.

19. **A positive therapeutic test is part of a complete course of treatment.** It should not be dropped when the diagnosis is made.

20. **Never end indeterminate therapeutic tests with arsphenamin.** You may leave the patient with the immunity, that has kept the disease concealed, broken by your inadequate treatment. Give at least forty inunctions or their equivalent.

Early Diagnosis of Syphilis of the Heart. Angina Pectoris. Gastric Symptoms. Symptomatic Relief Under Treatment with Subsequent Appearance of Physical Signs of Aortitis Possibly Due to Healing.

Case 190,150, Man aged twenty-nine years, married, machinist.

4/3/17 Examined.
No History of Syphilis primary or secondary.
Gonorrhea five years ago.
Duration of Symptoms: Six months.
Onset: Heartburn, exhaustion, pain in stomach, back, and arms. Slight dyspnea, worse on exertion. Nocturia three times.

4/3/17 Physical Signs:
Apex heart seventh interspace.
Pulse, 69.
No murmurs (Willius).
Left pupil sluggish.
Knee-jerk accentuated.
Blood-pressure: Systolic, 130; diastolic, 100.
Electrocardiogram: Rate 69. Sinus bradycardia, left ventricular hypertrophy.
Urine normal.
Tonsils Septic.
Roentgenogram of Chest: Small calcified area right upper lobe.
Serum Wassermann Reaction moderately positive, followed by weakly positive reaction.
Consultant's Diagnosis: True angina pectoris 75 per cent. At this patient's age probably syphilitic.
Treatment: Five injections arsphenamin, six injections mercury salicylate.
Great improvement in anginal attacks and general condition.
5/19/17 Tonsillectomy.
8/25/17 Re-examined: Cardiac dilatation disappeared. No murmurs. Blood-pressure: Systolic, 115; diastolic, 65.
Treatment: Twenty more injections arsphenamin. Forty injections mercury succinimid. 160 inunctions, 4 gm. Mercury with chalk, gr. j, three times daily, 500 tablets. Potassium iodid, minims 10–30, 6 ounces.
Serum Wassermann Reaction:
9/24/18 Strongly positive.
10/10/18 Strongly positive.
Negative thereafter.
3/23/18 Spinal Fluid: Wassermann reaction negative. Nonne reaction negative, lymphocytes 5.
12/29/20 Re-examined: Heart 9.5 cm., regular. No capillary pulse. Blood-pressure: Systolic, 120; diastolic, 70. Pulse-rate 70.
Anginal pains have completely disappeared, even with exertion. No dyspnea.
Soft Blowing Diastolic Murmur Over Aa. Not heard in carotids or femorals.

Discussion

1. **To be effectively treated** syphilis of the heart and aorta should be recognized before the appearance of valvular incompetency. A number of observers have emphasized this fact.

2. **The symptoms of slight coronary sclerosis** often **precede** the appearance of **signs.**

3. **The Wassermann reaction is more apt to be positive** at this early stage than later.

4. **The treatment should be begun with mercurial preparation,** but subsequently arsphenamin and mercury should be pushed with vigor.

5. **The recognition of a murmur after three years of treatment** may probably be interpreted as a result of sclerotic changes in a healed aorta and valve, rather than evidence of a refractory or advancing process.

6. **We have seen much evidence that healing changes actually take place** in the cardiovascular system, which if too rapid give rise to serious complications. If the changes are gradual they may result in the appearance or accentuation of physical signs.

"Tumor of Mediastinum." Unfavorable Progress Under Treatment. Development of Pulsating Tumor, Showing Mass to Be an Aneurysm.

Case 239,085, Man aged forty-eight years, married, laborer.

6/19/18 Examined.
Gonorrhea twenty-five years ago. No history of chancre or secondaries.
Duration of Symptoms: Eighteen months.
Symptoms:
Pain in left shoulder.
No cough.
No voice changes.
Abscess (?) over left scapula opened eighteen months ago.
Physical Signs:
Restriction of movement, left chest.
Dilatation of superficial veins.
No visible tumor.
No murmur, thrill, pulsation, or tug.
Palpable glands, both axillæ.
Scar over left scapula.
Roentgenographic and Fluoroscopic Examination: *No pulsation.*
"Tumor of mediastinum, probably sarcoma."
Serum Wassermann reaction moderately positive.
Treatment: Rest in bed one week with
Mercurial preparation; Six inunctions, four injections mercury succinimid; potassium iodid by mouth.
Arsphenamin; 0.3 gm., 0.4 gm., 0.5 gm., 0.3 gm. at weekly intervals.
No Relief: Loss of weight 16 pounds in six weeks.
Pulsating Tumor appeared with third injection arsphenamin at inner border left scapula and increased rapidly in size. Complete relief from pain.
Tracheal Tug appeared. Aneurysmal pulsation now demonstrable by fluoroscope.

DISCUSSION

1. **The roentgenographic diagnosis of malignancy** was supported by palpable glands.

2. **Not every mediastinal mass that does not show pulsation is a solid tumor,** nor is every mediastinal mass with an associated partial positive Wassermann reaction a manifestation of syphilis. Exploration has demonstrated sarcoma pathologically. In general, however, a therapeutic test should precede exploration.

3. **A therapeutic test for syphilis may demonstrate an aneurysm** previously unrecognizable. Such tests must be made with a prolonged mercurial and iodid preparation.

4. **Two weeks of inunctions is not an adequate mercurial preparation.** Four to six weeks is better.

5. **The rapid tissue change and the possible serious effects** induced in late syphilitic lesions by modern treatment for syphilis are well illustrated by this case. This patient (compare also Case 299,972) should have had several weeks of rest in bed on mercurial and iodid preparation, with arsphenamin later, rather than a therapeutic shock from such a rapid-acting vasculotoxic drug as arsphenamin at the outset. The initial dosage of arsphenamin was excessive. We have learned to prefer neo-arsphenamin 0.05 to 0.4 gm. in ascending dosage, with weekly intervals.

6. **The change in the roentgenologic and physical findings** which appeared after the third week suggests late healing rather than early Herxheimer effect. The pulsation, visible tumor, etc., previously unrecognizable, appeared presumably with the weakening of the vessel wall and the resolution of the peri-aortitis and mediastinitis which had caused the fixation and supported the vessel.

7. **Provocative procedures may be dangerous** in mediastinal conditions (Case 299,972).

8. **Treatment seldom produces much visible change in aneurysms.**

Subdiaphragmatic Aortic Aneurysm. Rupture Following First Arsphenamin Injection.

Case 299,972, Man aged forty-six years, single, hotel clerk.

12/17/19 Examined.
"Chancroid" Twenty-one Years Ago: Local treatment only.
Duration of Symptoms: Eleven months.
Onset sudden. Previously good health.
Symptoms:
Pain, epigastric, shooting and aching, day and night, worse with the patient recumbent, relieved by soda.
Vomiting accompanying the pain.
Periodic attacks of symptoms every three or four days, six to seven seizures a day.
Physical Signs:
Blood-pressure: Systolic, 170; diastolic, 95.
Murmur, diastolic, occasional.
First sound, snapping.
Bruit, below ensiform cartilage, loud.
Pulsation, site of bruit.
Roentgenographic and Fluoroscopic Examination of Thorax negative (except for slight indentation of right lobe of liver).
Signs of Hypertrophic Arthritis, lumbar spine.
Urine: Much albumin and many casts, occasional blood-cells.
Serum Wassermann Reaction strongly positive.
Diagnoses:
Radiculitis from pressure (neurologic).
Parenchymatous nephritis.
Syphilis: Aneurysm of the abdominal aorta (?).
Treatment:
Arsphenamin: One injection 0.2 gm. intravenously.
Complications: Increased pain for twenty-four hours.
Collapse and death in forty-eight hours.
Necropsy:
Subdiaphragmatic aneurysm 10 cm. in diameter ruptured into abdominal cavity. Advanced atheromatous and calcareous changes. Kidneys, cloudy swelling.

Discussion

1. **The predominance of gastric symptoms is striking,** and almost suggests gastric crises or uremia. Cabot has pointed out the prominence of cardiac disease as a cause of gastric symptoms. They are also a conspicuous element in the symptomatology of late syphilis.

2. **The shooting pain suggested tabetic neurosyphilis.**

3. **The aneurysm projected anteriorly** and was so high as to be practically invisible behind the overlapping liver.

4. **The diagnosis of aneurysm was qualified** by the negative Roentgen-ray and fluoroscopic findings. The spondylitis might explain the pains.

5. **The nephritis was suspected of being syphilitic,** although it was late in the disease for such a manifestation. This led to withholding mercury and initiating treatment with arsphenamin.

6. **That arsphenamin was responsible for the death of the patient** is suggested by the symptomatic flare-up after one injection.

7. **Such a case is a warning** of the danger of the provocative procedure (one arsphenamin injection, seven successive blood tests) in patients obviously suffering from an acute process.

8. **Arsphenamin makes a dangerous beginning** for treatment in late syphilis. The outlook in this case, though poor, might have been bettered by the use of a mild mercurial and iodid preparation (mixed treatment by mouth while at rest).

Aortitis with Angina Pectoris (Coronary Sclerosis). Serum Wassermann Reaction Deceptive. Associated Grave Neurosyphilis Recognized Only by Routine Spinal Puncture. Unfavorable Response to Routine Arsphenamin Treatment.

Case 339,443, Man aged thirty-four years, divorced, pool hall owner.

10/30/20 Examined.
Gonorrhea and Hard Sore twelve years ago. No secondaries. No treatment.
Duration of Symptoms: Two years.
Onset: Pain in the left breast during exertion.
Symptoms:
Attacks of pain in left breast and arm produced by exertion, relieved by rest.
Stomach trouble, palpitation, "gas."
Dyspnea moderate.
Physical Signs:
Those of advanced aortitis.
Probable coronary sclerosis.
Blood-pressure: Systolic, 120; diastolic, 40.
Pupils and reflexes negative.
Serum Wassermann Reaction weakly positive (one); negative on repetition (six).
Treatment: Begun on diagnosis of syphilitic aortitis and coronary sclerosis.
Mercurial preparation: Twelve inunctions and iodid. Stomatitis developed. Improved by dental extractions.
Arsphenamin (606): Five injections 0.2 to 0.4 gm. at weekly intervals.
Mercury succinimid: Twenty-one daily injections.
Routine Spinal Fluid Examination performed with second arsphenamain injection. Wassermann reaction + + + to 1 c.c., Nonne reaction positive, 94 lymphocytes, gold sol. 4433222100.
Patient Grew Progressively Worse with each arsphenamin injection until the fifth, when he could scarcely walk a block without bringing on an anginal attack.
Immediate improvement following suspension of arsphenamin therapy (two weeks).
Intraspinal Therapy: Two injections with little effect. Repeated paretic gold sol. curves. A detailed neurologic examination was overlooked. There were no gross changes.

Discussion

1. **The use of routine dosages and treatment methods** adapted to robust patients on such a heart, even though not decompensated, was evidently dangerous, and was followed by new anginal exacerbations.

2. **Active early neurosyphilis shown only by the spinal fluid** not infrequently occurs with a negative neurologic examination (incomplete in this case).

3. **Such a heart would have made intravenous therapy, sufficiently intensive to arrest the neurosyphilis, hazardous and difficult.**

4. **Neo-arsphenamin should have been used instead of arsphenamin** in 0.05 to 0.4 gm. doses, with Swift-Ellis intraspinal treatment, and rest in bed. The mercury preparation, while inadequate, possibly prevented a fatal outcome, but should have been longer and more intensive.

5. **Note the deceptive serum Wassermann tests** and the use of the Wassermann series to avoid the possible effect of a provocative dose.

6. **The value of routinely examining the spinal fluid of syphilitics** and suspected syphilitics in the absence of direct contraindication, regardless of their symptomatic pictures, is well illustrated. An earlier spinal fluid test would have disclosed the gravity of this case.

Cardiovascular Syphilis and Neurosyphilis. Death Under Treatment. Advanced Coronary Sclerosis of a Grade Not Suspected During Life.

Case 341,607, Woman aged thirty-five years, married, housewife (husband a garage mechanic).

11/22/20 Examined.
No History of Primary or Secondary Syphilis.
One Miscarriage.
Duration of Symptoms: Ten years.
Onset gradual, with vomiting during the first two years.
Symptoms:
Precordial pain, steady, moderate, non-radiating.
Fatigue.
Dyspnea, two years' duration.
Cough, nocturnal, choking.
Palpitation, tachycardia, five years.
No definite anginal attacks.
No edema or anasarca.
Physical Signs:
Heart greatly enlarged.
Auricular fibrillation.
Ventricular extrasystole.
Murmurs, systolic, diastolic.
Thrill, aortic area.
Pistol shot. Corrigan and capillary pulse.
Blood-pressure: Systolic, 140, *Diastolic not obtainable.*
Urine normal.
Spinal Fluid, Wassermann reaction *positive*, Nonne reaction negative, *42* lymphocytes.
Neurologic Signs: Pupils irregular, unequal, but reacting well. Few sensory, but no important reflex changes.
Treatment: Rest in bed with mercurial preparation for arsphenamin.
Mercurial preparation: Ten injections mercury succinimid ($\frac{1}{6}$ gr. daily) intramuscularly.
Arsphenamin: Injections 0.2 gm., 0.4 gm., 0.3 gm., 0.3 gm. intravenously at weekly intervals, begun after tenth injection succinimid.
Succinimid continued to twenty injections.
Improvement marked: Dyspnea, pain, and fibrillation disappeared; heart reduced in size.
Patient Died Suddenly in Bed six hours after fourth arsphenamin injection.
Necropsy: Far advanced aortic valvulitis; valves reduced to stubs. *Total obliteration left coronary artery.* Only a fibrous cord with a few sacculations could be found.

Discussion

1. **In advanced grades of valvular involvement the involvement of the coronaries may be expected to be severe. The symptoms may not be a guide. Even in mild grades of aortitis coronary changes may be so severe as to menace life.**

2. **Coronary involvement may be severe** without definite anginal attacks.

3. **A careful estimation of life expectancy** is a valuable element in deciding the treatment applicable to a given case.

4. **The combination of cardiac and neurosyphilis is not rare.**

5. **The risk is always great,** the cardiac condition, because it limits treatment, being the more serious element. Prognosis is, to some extent, proportional to the severity of the heart lesion. The cardiac symptoms may completely dominate the case and overshadow the neurologic symptoms.

6. **This patient was a wreck.** Cardiac dilatation, fibrillating auricle, and low diastolic pressure are warnings of the hopelessness of the case, the extent of structural damage, and the impossibility of attaining radical results.

7. **This patient was overtreated.** Mixed treatment by mouth with rest in bed for weeks might have prolonged life; probably it would not have affected the neurosyphilis.

8. **Arsphenamin, because it administers a therapeutic shock (Herxheimer reaction), because of the rapidity of the healing changes it produces, and because of its vasculotoxicity, is dangerous to bad hearts.**

9. **The arsphenamin dosage was too large** for such a case, and neoarsphenamin was probably to be preferred. The first dose should not exceed 0.05 gm., the last, 0.4 gm.

10. **The treatment of the neurosyphilis should have been secondary.** If the cardiac condition ever improved enough to warrant it, intraspinal measures should have been used.

11. **Intraspinal treatment after a long mercurial preparation is the method of election** in combined neurosyphilis and cardiac syphilis.

TREATMENT OF CARDIOVASCULAR SYPHILIS

Cases 190,150, 239,085, 299,972, 339,443, and 341,607, by the discussion of the individual cases, illustrate various phases and principles in the treatment of syphilis in the cardiovascular system. While it is customary for writers to recommend the use of arsphenamin and mercury in the treatment of this type of syphilitic involvement, an exact and widely applicable technic is only just in the process of being worked out. This technic must take account of the well-known toxic effect of arsphenamin on the vascular system, and of the fact that involvement of the heart and its intrinsic circulation in particular may be more serious than any visceral sign or symptom will indicate. Treatment must also reckon with the dangers of the therapeutic shock induced by a powerful drug such as arsphenamin, with the not always beneficial effects of rapid healing, and with the readjustments of balance in physiologic activity which this involves.

The remaining 5 cases, with their discussions, illustrate the confusion of gummatous lesions with tuberculosis and sarcoma, the diagnostic problem presented by the tonsillar chancre and secondary syphilitic lesions in the throat, and the etiology and therapeutic control of exfoliative dermatitis following arsphenamin administration.

Gumma of the Tongue Confused with Tuberculosis. Uncertainties in the Pathologic Diagnosis of Syphilis from Tissue.

Case 322,945, Man aged thirty-three years, married, civil engineer.

7/3/20 Examined.
Chief Complaint: Sore tongue.
History of Exposure to Tuberculosis. (Aunt had "galloping" consumption.)
Patient Said to Have Had Tuberculous Glands at twenty-two years of age. This condition cleared up quickly with *x*-ray, no suppuration, total duration six weeks.
History of Chronic Cough.
Penile Lesion at Twenty-one Years of Age, three weeks post coitu (note time relation to glands).
No Secondary Eruption.
Swollen Testicles, first right, then left, at twenty-eight years of age, two years' duration.
Married Six Years, Wife Well, No Miscarriages.
Onset of Present Trouble one year ago.
Symptoms: Tumor left side of dorsum of tongue. Slight ulceration. No glands.
Tumor Excised: Healed without incident.
Pathologic Diagnosis: *Tuberculosis.*
New Lesion Appears on the right side of the tongue just behind circumvallate papillæ. Deep nodule with slight superficial ulceration.
7/3/20 Entered Clinic.
Physical Signs: Pulmonary and roentgenographic evidence old tuberculosis left apex.
Sputum Twice Negative.
Serum Wassermann Reaction *strongly positive,* two examinations. Patient had never had a Wassermann test before.
Spinal Fluid negative.
Treatment:
In spite of the pathologic diagnosis of tuberculoma operation was postponed for a therapeutic test.
Mercurial preparation fourteen daily injections mercury succinimid. No iodid.
Lesion definitely smaller with seventh injection. Healed with fourteenth.
Arsphenamin; Routine treatment was then begun. Uneventful course. Wassermann reaction reversed after two series of six injections each. No recurrence.
Diagnosis: *Gumma of the tongue.*

Discussion

1. **The pathologic differentiation of tuberculosis and gumma is untrustworthy** unless characteristic tubercles and bacilli can be found.

2. **A diagnosis should never be made on a tumor of the tongue without a Wassermann test.** The physician in this case excised tissue and made a diagnosis without this test.

3. **A specimen for diagnosis should always be taken** whether the Wassermann reaction is positive or negative. A gumma readily undergoes malignant change.

4. **A positive Wassermann reaction may occur in tuberculosis,** but it is usually only partial, and seldom follows a typical course under treatment.

5. **The situation and appearance of this lesion were classical for gumma;** a deep mass, slight secondary ulceration, to one side of the median line, near the circumvallate papillæ. Ulceration may often be absent.

6. **The tuberculous adenitis may have been syphilitic** (short duration, no softening, too easy response, no relapse, occurred within a year after a probable chancre).

7. **The testicular involvement might well be syphilitic.**

8. **The pulmonary process may have been syphilitic.**

9. **Only a mercurial therapeutic test can be used to differentiate gumma from tuberculosis,** since arsphenamin has marked non-specific effects on the latter.

Gummas of the Jaw and Palatine Bones. Pathologic Diagnosis "Round-cell Sarcoma." Operation with Recurrence. Recovery Under Treatment for Syphilis.

Case 108,704, Schoolboy aged nine years.

6/23/14 Examined.
No History of Syphilis. Mother had two miscarriages, four living children.
Duration of Symptoms: Six months.
Onset: Tumor in right side of mouth.
1/20/14 Operation, bone scraped.
Lesion Recurred in One Month.
3/17/14 Second Operation, more dead bone and scrapings removed.
Tissue Examined microscopically. Pathologist reports *round-cell sarcoma.*
Lesion Recurred in Six Weeks.
6/23/14 First Examination in Clinic.
Tissue Again Removed for Diagnosis. No sarcoma found. Inflammatory tissue only.
Serum Wassermann Test not made.
10/20/14 Two Arsphenamin Injections elsewhere, and mercury by mouth.
Some improvement.
1/19/15 Swelling Lower End Right Humerus. Roentgen-ray report "looks specific."
Mercury Rubbed on Locally.
3/29/15 Serum Wassermann Reaction strongly positive.
3/30/15 Seven Injections Arsphenamin, weekly intervals, 0.05 to 0.2 gm.
Improved: Serum Wassermann reaction strongly positive.
Mother's Serum Wassermann Reaction negative.
9/1/16 Relapse While on Inunctions during war scarcity of arsphenamin. Much deformity developed. Perforation of palate, septum destroyed.
9/22/16 to 5/28/17 Twelve Injections Arsphenamin: 0.3 to 0.5 gm. Sixty 3 gm. 33 per cent. inunctions. Potassium iodid, minims 10, 6 ounces.
Process arrested, serum Wassermann reaction negative.

Discussion

1. **Syphilomas before healing sets in seem to be rather easily confused histologically** with the pathologic picture of round-cell sarcoma and lymphosarcoma. A Wassermann test and a search for further evidence of syphilis will sometimes prevent an error in diagnosis and needless operative interference.

2. **The local use of mercury** on a lesion (1/19/15) is no substitute for systematic use of mercury by a good inunction technic.

3. **Note the inability of inunctions alone to hold the process in check** (9/1/16). This, in my experience, is not uncommon in bone syphilis. The synchronous use of arsphenamin and mercury in resistant cases will sometimes accomplish results not obtainable with either alone.

4. **The earlier arsphenamin dosage** (0.05 to 0.2 gm.) **was inadequate.**

5. **The mother did not have an adequate examination.** She subsequently developed a nodular lesion on the cheek.

Gumma of the Lymph-nodes, Confusion of Tuberculosis and Syphilis. Effect of Arsphenamin on Optic Atrophy.

Case 277,930, Woman aged twenty-four years, housewife (husband a butter-maker).

6/30/19 Examined.
No Definite History of Syphilis. Divorced six months after marriage to a "brute."
Duration of Symptoms: One year.
Onset: Mass in submaxillary region developed after tonsillitis.
Mass Excised Elsewhere, but lesion did not heal.
Operation Repeated Elsewhere: Lesion healed.
Lesion Reopened Spontaneously (injury with pin four weeks ago).
Physical Signs:
Mass suggesting matted glands below the ramus of the right jaw.
Sinuses with ulceration.
Arciform lesion along border of scar.
Serum Wassermann Reaction strongly and repeatedly positive.
High Myopia with Primary Optic Atrophy.
Cerebrospinal Fluid negative except for 8 lymphocytes.
Bárány Test Positive.
Neurologic Examination negative.
Treatment:
Arsphenamin; Five injections 0.3 to 0.4 gm. without preparation at weekly intervals. No local flare-up (Herxheimer reaction). Healing slow.
Eyes Grew Rapidly Worse During Course. Sixth injection omitted. Lesion only partly healed on dismissal.
Lesion healed completely while at home on forty inunctions.
Another Arsphenamin Injection Four Months Later Made the Eyes Markedly Worse ("Like a Cloud"). Fundus examination: Optic atrophy is progressing. Patient can tolerate 1 to 2 dg. doses of arsphenamin fairly well. Eyes stationary under mercury.

Discussion

1. **If the surgeon had had his suspicions aroused by the marital history and had made a Wassermann test** the patient might have been spared two unsuccessful operations for gummatous instead of tuberculous glands.

2. **Gumma of the lymph-nodes may come on after tonsillitis** precisely as in the case of tuberculous glands.

3. **The bubo of a tonsillar chancre should be considered** in the differential diagnosis. The satellite bubo does not break down.

4. **False positive Wassermann results** (usually + or + +) may occur with tuberculous glands.

5. **Tuberculous glands with sinuses may heal under arsphenamin,** even in the absence of syphilis—a false positive therapeutic test.

6. **The pathologic differentiation of gumma and tuberculoma is not** always trustworthy.

7. **It may be impossible to make a differential diagnosis** of syphilis and tuberculosis in certain cases without prolonged observation.

8. **Look for a tuberculid on the skin** which will sometimes unexpectedly clinch the diagnosis.

9. **As evidence for syphilis,** the prominence of the cutaneous lesion as compared with the glandular lesion, the repeated positive Wassermann reaction over a period of months with final reversal under treatment, the slightly abnormal spinal fluid, and the positive Bárány findings (inflammatory process of the brain stem) all deserve mention.

10. **It may incidentally be observed that primary optic atrophy,** from whatever cause, may sometimes respond unfavorably to arsphenamin.

Tonsillar Chancre (?). Tonsillectomy. Cervical Adenitis. Possible Erroneous Interpretations Due to Incomplete Examination.

Case 298,078, Girl aged nineteen years.

11/29/19 Examined.

Nose and Throat Specialist's Examination:

Chief Complaint: Tonsillitis, swollen glands.

10/15/19 Tonsillitis, severe.

11/1/19 Tonsillectomy (?). Glands did not subside. No pain or tenderness.

11/29/19 Otolaryngologist's Examination (verbatim): "Small ulcer with pus, upper part of hard palate. Tonsils 3 (large) right. Large left stub with much induration. Soft plugs right; marked granular pharyngitis; mucopurulent material in nasopharynx. Nose and ears nothing of note. Gland, size of walnut, right cervical region.

"Summary: question of lymphosarcoma or Hodgkin's. Wassermann test to rule out syphilis. Does not resemble tuberculous glands. History of repeated attacks of tonsillitis each winter. General health good."

Transferred to Syphilologist when Serum Wassermann Reaction was Found to be Strongly Positive.

Dermatosyphilographer's Examination:

Chief Complaint: Positive Wassermann reaction and sore throat with glandular involvement.

11/30/19 Differential count negative.

12/2/19 Syphilologic Examination (verbatim): "Cervical adenitis described. Hair thinned. Small patches of depigmentation on neck. Across upper extremities, shoulders and upper thorax, a faint maculopapular eruption, only visible by cross illumination. Apparently involuting roseola.

"*Genitalia:* Right labium majus, several small eroded papules and a large irregular ill-defined indurated plaque size of dime. Labia minora eroded.

"*Mucous membranes:* Erosion of hard palate, dark field positive for *Spirocheta pallida.* Mucous patch left anterior pillar.

"*General adenopathy.*

"*Vaginal introitus intact.*

"Genital lesions present one and one-half weeks."

DISCUSSION

1. **The two examinations are paralleled and quoted verbatim to show the difference in point of view.**

2. **Persistent painless cervical adenitis associated with a throat or lip lesion** should arouse a suspicion of syphilis and lead to an investigation by dark field, gland aspiration, Wassermann tests, and complete physical examination.

3. Specialists whose work is sharply limited to a particular region or group of structures are especially prone to overlook syphilis by missing its collateral manifestations. Every specialist should make a rapid general examination by a good light if he wishes to recognize the syphilis which passes through his hands.

4. **This patient sustained a partial tonsillectomy for a probable tonsillar chancre,** and her medical adviser proposed an excision of the glands, constituting the satellite bubo of her tonsillar chancre, on a presumptive diagnosis of tuberculosis, **because he overlooked the possibility of syphilis.** The otolaryngologist did not place the possibility of syphilis first instead of last, because he did not see the skin and genitalia. He suspected lymphosarcoma or Hodgkin's disease.

5. **The intact vaginal introitus does not prove a tonsillar chancre as against a genital chancre.** Mere contact without consummation of intercourse may result in infection (Case 163,665). The circumstances of the case and the cervical adenitis make a tonsillar primary lesion the stronger probability.

6. **Many tonsillar chancres are operated on each year** through failure (1) to suspect cervical adenitis of being a satellite bubo; (2) to order a dark field on an erosion; (3) to consider syphilis before diagnosing Vincent's angina; (4) to make a Wassermann test on every patient with a bad throat; and (5) to inspect the skin by a good light in every patient with a bad throat.

Control of Exfoliative Dermatitis Following Arsphenamin Administration.
Association with Intercurrent Infection and Local Irritation (Inunctions).
Case 338,505, Woman aged forty years, widow, boarding-house keeper.

10/22/20 Entered Clinic with a Maculopapular Secondary Syphilid: History of exposure, duration of infection not known. Serum Wassermann reaction + + +.
Cough Since Childhood of increasing severity during the last two years.
Pain in Chest, Hoarseness, Roentgenogram Shows Tuberculosis of the Left Upper Lobe: Sputum negative. A few coarse râles. Temperature normal. No loss of weight.
First Arsphenamin Injection: 3 dg. Vomited. Secondary syphilid disappearing.
Second Arsphenamin Injection: 3 dg. four days later. No reaction.
Four days later, pharyngitis, tonsillitis, palpable cervical glands, hacking cough, audible rhonchi, nose running, temperature 101° F.
Papular Dermatitis on arms and legs, face swollen. *Patient had not received any mercury.*
Put to Bed in Hospital: Given 500 c.c. Fischer's solution (hypertonic saline and sodium carbonate) by rectum. Temperature fell to normal in twelve hours.
Dermatitis Disappeared in Five Days.
Third Arsphenamin Injection: 1 dg. Given 500 c.c. Fischer's solution by proctoclysis in the following twenty-four hours. No complications.
Fourth and Fifth Arsphenamin Injections one and two weeks later, 2 and 3 dg.; Fischer's solution as before. No complications.
Sixth and Seventh Arsphenamin Injections: *3 dg., 4 dg. Through an oversight Fischer's solution was not given after the sixth and seventh injections.*
Dermatitis reappeared three days after the seventh injection without accompanying febrile or infectious symptoms, *following an attempt to begin inunctions* on the order of an inexperienced physician.
Typical Early Exfoliative Reaction Followed, controlled in ten days by:
Colloid bath, twenty minutes four times a day.
Potus imperialis by mouth.
Fischer's solution by rectum.
Lassar's paste (without salicylic acid) applied to the skin between baths.
Tonsils showed evidence of chronic infection at this time.

Discussion

1. **Intercurrent pulmonary tuberculosis** if not febrile and if the patient is in good condition makes more difficult, but does not contraindicate, intensive treatment for early syphilis. Do not use iodids.

2. **It has been contended that exfoliative dermatitis is especially frequent** following the combined administration of mercury and arsphenamin on the theory that mercury, by injuring the kidney, causes an arsenic retention. That this is not necessarily true is shown by the present case.

3. **This patient apparently was hypersusceptible** to arsphenamin at the outset.

4. **The first outbreak of dermatitis** was apparently precipitated by the intercurrent respiratory infection.

5. **The second outbreak** followed (*a*) failure to push the alkalinization and (*b*) the attempt to use inunctions on a hypersensitive skin.

6. **It was essential that this patient be carried through a full course of arsphenamin** to reduce the risk of neuro-recurrence in an early syphilis inadequately treated; otherwise the drug might have been abandoned.

7. **Patients obviously hypersensitive to arsphenamin** must be given mercury with the greatest caution, if at all, during the intravenous course, and *never in the form of inunctions.* Mercury salicylate and other insoluble mercurials intramuscularly can also precipitate exfoliative dermatitis.

8. **By the technic outlined above,** plus the complete extirpation of all accessible foci of infection, especially in tonsils and teeth, patients can be carried through as many as twelve arsphenamin injections after the first warning of exfoliative reaction. Such a technic can only be applied satisfactorily in a properly equipped hospital under expert direction, and is not proposed for application to the conditions of ordinary practice.

TARDY PARALYSIS OF THE ULNAR NERVE

WALTER D. SHELDEN

IN January, 1918 a physician, thirty-one years of age, presented himself for examination in our service at the Clinic, complaining of numbness and weakness in the distribution of the right ulnar nerve. He had fractured the right elbow at the age of five, displacing the internal condyle downward and inward. This deformity carried the ulnar nerve to an exposed position at the apex of the displaced fragment. Trivial injuries to the nerve had been very frequent and it has been unusually tender. Twice in the two months before the examination it had been injured slightly at the elbow, since which numbness, weakness of the small muscles in the hand, and atrophy had been noted. The patient was unable to spread and close the fingers normally. Paresthesia was induced by flexion of the forearm, producing notable tension on the nerve. At the elbow the ulnar nerve showed a fusiform enlargement for about 5 cm.

It occurred to us that elimination of the symptoms might be accomplished by transferring the nerve anterior to the interior condyle, and the operation was performed. The function of the nerve improved greatly, so that the patient is able to do his work without hindrance. The atrophy has largely disappeared. The nerve is definitely movable in the new position and has lost its former tenderness. A recent letter states that the arm is fully restored to its former usefulness.

We have observed 22 cases of a similar nature, in 15 of which operation was performed. The relative frequency with which we observed this syndrome awakened our interest and prompted me to present our experience with it.

In Tables I and II an attempt is made to present the important facts with regard to the 22 patients under discussion;

TABLE 1

CASES OF TARDY PARALYSIS OF THE ULNAR NERVE IN WHICH OPERATION WAS PERFORMED

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Condition of nerve at operation.	Answer to questionnaire.
Case I 82,214 M., 31	Fracture at five years; symptoms for two months. 1/15/18 Examination.	Deformity of right elbow. Internal condyle displaced inward. Nerve on apex of displaced condyle. Flexion increases symptoms.	Atrophy, +1 Strength, −2 Responses: Pain, −2 Touch, −2	Size, + Consistency, + Tenderness, +2	1/17/18 Nerve enlarged 0.3 cm. Small neuroma.	9/4/20 Use of arm: "O. K. except for heavy work. Strength: One-half due to deformity of old fracture. Atrophy: Slightly, always. Pain: Only from heavywork. Tingling: Only when used too much. Numbness: Slight in little finger. Other symptoms: No."
Case II 220,582 M., 42	No injury; symptoms for four or five years. 1/30/18 Examination.	Roentgenogram negative for cervical ribs, shoulder, and elbow on right.	Atrophy, +3 Strength, −3 Responses: Pain, −2 Temperature, −2 Touch, −2	.....	2/9/18 Nerve enlarged for 3.7 cm. Bony overgrowth from ulnar encroached on nerve at point of elbow. Pseudoneuromas.	1/5/21 Use of arm: "As well as ever. Strength: Not as strong as the other arm. Atrophy: No. Pain: No. Tingling: No. Numbness: No. Other symptoms: Better color and not as small as two years ago."
Case III 222,410 F., 32	Fracture of left elbow at nine years and elevenyears;symptoms for five years. 2/16/18 Examination.	Marked deformity of left elbow. Fracture of outer condyle.	Atrophy, +3 Strength, −3 Responses: Pain, −3 Temperature, −3 Touch, −3	Size, +3 Consistency, +2	2/23/18 Nerve 0.8 and 0.5 cm. in diameter. Pseudoneuromas enlarging at point of elbow.	1/5/21 Use of arm: "Nearly as good as other arm. Strength: Very satisfactory. Atrophy: Some, but there has been great improvement. Pain: No. Tingling: No. Numbness: Slight in little finger. Other symptoms: No."

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Condition of nerve at operation.	Answer to questionnaire.
Case IV 250,854 M., 34	Fracture at two years; symptoms for ten months. 11/3/18 Examination.	Deformity of left elbow.	Atrophy, +3 Strength, −3 Responses: Pain, −2 Temperature, −2 Touch, −2	Size, +2 Partial reaction of degeneration. Tenderness, +2	11/15/18 Size one and a half times normal. One small pseudoneuroma with fusiform thickening.	8/24/20 Use of arm: "Constant. Strength: 75 per cent. Atrophy: Yes, better. Pain: No. Tingling: No. Numbness: No. Other symptoms: No."
Case V 250,349 M., 28	Fracture of right elbow at ten years and twenty-eight years; symptoms for one month. 11/6/18 Examination.	Deformity of right elbow. Fracture callus of inner condyle. Mass 1 cm. in diameter attached to or near nerve 2.5 cm. below point of elbow.	Atrophy, +2 Strength, −2 Responses: Pain, −3 Touch, −3	Size, +2 Consistency, +2 Tenderness, +	11/30/18 Size one and one-eighth times normal. Nerve pressed aside by bursa.	11/4/20 Use of arm: "Good as before last injury. Strength: Not quite so strong as other arm. Atrophy: No. Pain: Only following hard work. Tingling: No. Numbness: No. Other symptoms: No."
Case VI 253,421 M., 42	No injury; rheumatismal pain in right elbow for some years; symptoms for three months. 12/13/18 Examination.	Marked bony overgrowth with deformity extension 120°. Shallow ulnar groove.	Atrophy, +3 Strength, −3 Sensibility, −2	.....	1/17/19 Small thickening.	8/24/20 Use of arm: "Very well. Strength: Nearly as strong as left arm. Atrophy: Yes, never filled in quite. Pain: No. Tingling: No. Numbness: Yes. Other symptoms: No."
Case VII 253,903 M., 39	Fracture at thirty-eight years; symptoms for two months. 12/18/18 Examination.	Range movement at right elbow 90°. Destruction articular cartilage. Loose foreign body over head of radius, one over coronoid process of ulnar. Deformity of	Atrophy, +3 Strength, −3 Responses: Pain, −4 Temperature, −4 Touch, −4	Size, + Consistency, + Tenderness, +	12/27/18 Removal of both foreign bodies. Large bursa in ulnar groove 1.8 by 1.2 cm. One pseudoneuroma.	1/5/21 Use of arm: "Very well for any kind of labor. Strength: 90 per cent. Atrophy: Difference scarcely noticeable. Pain: At times at elbow, but slight.

TABLE I (continued)

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Condition of nerve at operation.	Answer to questionnaire.
Case VII continued		ulnar groove; filled; firm and hard (roentgenogram).				Tingling: Yes, in little finger. Numbness: Sometimes at night. Other symptoms: Sometimes a catch at the elbow and on straightening a cracking is felt, relieving the catch."
Case VIII 254,397 M., 45	Fracture at seventeen years; symptoms for many years. 12/27/18 Examination.	Deformity of internal condyle, right elbow.	Atrophy, (?) Strength, −2 Responses: Pain, −3 Touch, −4	Size, +3 Consistency, +3 Tenderness, +1	1/11/19 Marked inflammatory interstitial neuritis, 3.7 cm. Two small neuromas. Ulnar groove shallow from overgrowth of bone about internal condyle.	8/24/20 Use of arm: "No better. Strength: Not nearly as strong. Atrophy: Yes. Pain: Yes. Tingling: Yes. Numbness: Slight in little finger. Other symptoms: No."
Case IX 256,920 F., 38	Fracture of right elbow at six years; symptoms for eight years. 1/20/19 Examination.	Right arm inferior developmentally. Fracture outer condyle with loose fragment. Range at elbow 100°.	Atrophy, +3 Strength, −2 Responses: Pain, −4 Temperature, −3 Touch, −4	.....	1/28/19 Interstitial neuritis, epineurium incised by several incisions for constricted areas.	8/24/20 Use of arm: "Some better. Strength: Questionable, fair in hand. Atrophy: Think not. Pain: Quite severe under side of arm; improving. Tingling: Yes. Numbness: At times; improving. Other symptoms: Feel cord where operated; arm weaker and harder to use."
Case X 264,881 F., 24	Fracture at three years; symptoms for four months. 3/22/19 Examination.	Deformity of left inner condyle; shallow ulnar groove.	Atrophy, +1 Strength, −1 Responses: Pain, −2 Temperature, −3	Size, +2 Consistency, +1	4/1/19 Diffuse thickening for 5 cm. Pseudoneuroma involving one-third of nerve.	9/15/20 Use of arm: "Normal. Strength: Slightly less than other arm. Atrophy: Very little. Pain: No.

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Condition of nerve at operation.	Answer to questionnaire.
Case X continued			Touch, −2		Inflammation.	Tingling: No. Numbness: No. Other symptoms: No."
Case XI 272,370 M., 43	Fracture at twelve years; symptoms for six months. 5/26/19 Examination.	Deformity of right elbow. Extension 65°. Internal condyle displaced backward and laterally.	Atrophy, +1 Strength, −1 Responses: Pain, −4 Temperature, −4 Touch, −2	Size, +2 Nodular.	6/7/19 Size one and a half times normal. Two pseudoneuromas with diffuse thickening for 5 cm. over point of elbow.	8/24/20 Use of arm: "Pretty well. Strength: Not quite as well. Atrophy: Yes. Pain: Elbow to wrist. Tingling: No. Numbness: No. Other symptoms: No."
Case XII 230,109 M., 47	Fracture at twelve years; symptoms for eight months. 10/3/19 Examination.	Deformity of left elbow, internal condyle prominent.	Atrophy, +3 Strength, −3 Responses: Pain, −4 Temperature, −4 Touch, −2	Antibrachialis also affected.	10/11/19 Diffuse thickening for 5 cm. over point of elbow.	8/24/20 Use of arm: "Fairly well. Strength: About as strong as right. Atrophy: No more than at time of operation. Numbness: Considerable from hand to elbow. Other symptoms: No."
Case XIII 300,091 M., 62	Indefinite injury at fifty-two years; symptoms for twelve months. 12/19/19 Examination.	Hypertrophic arthritis of right elbow and wrist. Right flexion 10° past 90°; left flexion 20° past 90°. Right ulnar markedly involved, left ulnar slightly. Musculospiral nerve also.	Atrophy, +2 Strength, −3 Responses: Pain, −2 Temperature, −1 Touch, 0	Size, +2 Consistency, +1 Tenderness, +2 Tenderness of musculospiral nerve, +2	1/6/20 Fusiform thickening. Three small pseudoneuromas. Ulnar groove obliterated by bony overgrowth.	11/4/20 Use of arm: "About same as before operation. Strength: Fairly good. Can't lift things above shoulder. Atrophy: Same as before operation. Pain: A dull hurting, no sharp pain. Tingling: Almost constant in little and ring fingers. Numbness: Numbness in ulnar. Other symptoms: When hand gets cold it is almost powerless."

TABLE I (continued)

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Condition of nerve at operation.	Answer to questionnaire.
Case XIV 300,866 M., 30	Fracture at ten years; symptoms for two years. 1/26/20 Examination.	Decubitus valgus. Flexion 50°. Extension 150°. External condyle displaced upward.	Atrophy, +2 Strength, −1	Size, + Consistency, + Tenderness, +	3/30/20 Size one-half times normal.	12/4/20 Use of arm: "Can't work much. Strength: One-half. Atrophy: No. Pain: At elbow on action. Tingling: No. Numbness: Below ulnar. Other symptoms: No."
Case XV 311,912 M., 42	Fracture at four years; symptoms for ten years. 4/12/20 Examination.	Infectious arthritis of right elbow with partial ankylosis. Tonsillectomy for arthritis. Arthritis of spine and left elbow.	Atrophy, +2 Strength, −3 Responses: Pain, −2	Size, +2 Consistency, +1	5/1/20 Thickening for 2.5 cm. at elbow.	8/24/20 Use of arm: "Can't work with it. Strength: Weaker than other arm. Atrophy: Can't say. Pain: When bending. Tingling: Not if quiet. Numbness: Yes. Other symptoms: No."

TABLE II

CASES OF TARDY PARALYSIS OF THE ULNAR NERVE IN WHICH OPERATION WAS NOT PERFORMED

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Answer to questionnaire.
Case I 108,259 M., 30	Fracture and dislocation at four years; symptoms for three years. 6/16/14 Examination.	Deformity of left elbow. Arm underdeveloped. Old ununited fracture of outer condyle of humerus (roentgenogram).	Atrophy, +2 Strength, −2 Sensibility, −2	.....	9/15/20 Use of arm: "Use for all work requiring only ordinary grip. Strength: Much weaker than right arm. Atrophy: Gradual wasting. Pain: None except after exceptional work. Tingling: Scarcely any now. Numbness: Small and ring fingers partially numb. Other symptoms: No."
Case II 126,144 M., 40	Right elbow tapped twice at twenty-three years, multiple arthritis then; symptoms for one year. 3/9/15 Examination.	Deformity: old destructive arthritis with partial ankylosis (roentgenogram).	Atrophy, −2 Strength, +2 Sensibility, −2	Size, +2 Consistency, +2	9/18/20 Death from appendicitis.
Case III 224,203 M., 26	Fracture of right elbow at four years; symptoms for twelve years. 3/7/18 Examination.	Fracture of right condyle with loose body. Internal condyle fracture, deformity of right elbow, claw-hand (roentgenogram).	Atrophy, +3 Strength, −3 Responses: Pain, −2 Temperature, −3 Touch, −2	Size, +3 Consistency, +2 Nodular.	9/15/20 Use of arm: "About the same. Strength: About one-half that of the other arm. Atrophy: Increasing gradually. Pain: Yes. Tingling: Yes. Numbness: Yes. Other symptoms: Can't open hand as well as before."
Case IV 157,593 M., 61	Dislocation of left elbow at twenty-six years and of right elbow at twenty-eight years; symptoms for one year. 9/30/18 Examination. 9/29/20 Re-examination.	Deformity of both elbows, greater in the left. Multiple foreign bodies in both elbows, probably cartilages (roentgenogram).	Atrophy, +2 Strength, −3 Responses: Pain, −3 Temperature, −3 Touch, −3	Right. Left. Size, +1 +2 Consistency, +1 +2 Tenderness, +2 +1	9/29/20 Use of arm: "Same as at examination. Strength: About equal with other arm. Atrophy: Yes. Pain: Aching at elbow. Tingling: In fingers. Numbness: In fingers. Other symptoms: Cramps in little finger

TABLE II (continued)

Case, sex, age.	Injury and deformity.		Symptoms.	Condition of nerve.	Answer to questionnaire.
Case V 253,981 M., 29	Fracture of left elbow at six years; symptoms for one year. 12/19/18 Examination.	Deformity of left elbow and fracture of inner condyle and radius.	Atrophy, +3 Strength, −2 Responses: Pain, −2 Touch, −2	Size, +2 Tenderness, +2	9/15/20 Use of arm: "Three-fourth use. Strength: Three-fourth strength. Atrophy: Yes. Pain: Some when in use. Tingling: Yes. Numbness: Yes. Other symptoms: No."
Case VI[1] 292,093 F., 27	Fracture of right elbow at twelve years; symptoms for nine months. 10/6/19 Examination.	Fracture of radius and ulna. Pronation and supination impaired. Ankylosis.	Atrophy, +2 Strength, −1 Responses: Pain, −1 Temperature, −1 Touch, −1	Size, +2 Consistency, +2 Tenderness, +1	
Case VII 299,485 M., 51	Dislocation of right elbow at ten years; symptoms for thirty-one years. Improvement on change of work. Recurrence at forty-six years. 12/11/19 Examination.	.....	Atrophy, +3 Strength, −3	Size, +2 Consistency, +2	11/4/20 Use of arm: "Same as before. Strength: A little weaker than other arm. Atrophy: The same. Pain: At night when sleeping. Tingling: Sometimes. Numbness: At night. Other symptoms: No."

[1] Operation postponed because patient was four months pregnant.

15 were treated surgically and 7 expectantly. —1, —2, —3, —4 and +1, +2, +3, and +4 indicate the degrees of variation from normal, with 0 for normal. A questionnaire was sent to each patient on the date indicated at the head of the last column; the patients' answers are given in practically their own words.

Deformity of the elbow-joint constitutes the essential etiologic factor. In most instances the deformity results from fracture-dislocation of the elbow in childhood. Hypertrophic arthritis, foreign bodies in the elbow-joint, the development of bursa in the ulnar groove, and exostosis of the ulnar bone have brought about similar changes in the ulnar nerve with disturbance of its functions.

The average age at which a fracture-dislocation takes place is seven and a half years, while the average age at the appearance of the symptoms is about forty years. In one of our cases the lesion was bilateral, both elbow-joints being fractured. Usually the function of the arm is normal for a long period, except for disturbances such as arise from injury to the joint. Flexion and extension of the elbow-joint are often limited in degree, and the fracture impairs the development of the arm, as well as its strength and usefulness. In many patients paresthesia in the ulnar distribution has been noticed for many years; it is especially induced through too vigorous exercise of the elbow-joint. In one case the ulnar complaint had existed for eight years and in another for fifteen years. Remission of the symptoms is noted, especially if a light occupation is followed. Except for paresthesia and tenderness of the ulnar nerve, the first symptom to appear is atrophy of the small muscles of the hand, particularly in the first interosseous space. The atrophy is gradually progressive and with it is a corresponding weakness; the degree and rate of both are variable. Accompanying the atrophy and weakness are paresthesia and degrees of anesthesia to pain, temperature, and tactile sensibilities in the ulnar distribution of the hand. Almost without exception the ulnar nerve shows a spindle-shaped enlargement at the point of the elbow for about 5 cm., the diameter of which may be two or three times that of the normal nerve. Also, one or more nodules or circumscribed enlargements

may be found within the same district. Tenderness of the nerve at this point is not infrequent, and its consistency may increase and its mobility decrease. The deformity of the elbow may displace the nerve so that it rides on the tip of the elbow, or the ulnar groove may be so shallow that the enlarged nerve may be more prominent than the bony landmarks.

The electric examinations usually show a partial reaction or degeneration. Disturbance of the joint and sensibility to vibration were not present in our series of cases.

On exposure at operation the nerve shows a spindle-shaped enlargement from one to three times its normal diameter, and the nodules consist of thickening in the perineurium and connective tissue of the nerve. These swellings occupy a part, or at times the whole, diameter of the nerve and are firm. Occasionally injection of the blood-vessels is found, especially if hypertrophic arthritis produces deformity of the joint and if hypertrophic arthritis is more or less active in this and other joints. Occasionally the perineurium thickens to form a slight constriction.

The diagnosis offers no serious difficulty if in the presence of an ulnar nerve lesion due consideration is given to the deformity of the elbow-joint. The palpation of the nerve itself as it courses about the elbow is decidedly important, as in no lesion other than leprosy have we met with such characteristic changes as have been described.

TREATMENT

Rest and electricity have been employed with some success in the treatment of tardy paralysis of the ulnar nerve, especially after the abandonment of a laborious occupation, which subjects the nerve to unusual and frequent tension and to slight and frequent traumatism. Resection of the damaged portion of the ulnar nerve, cuneiform resection, deepening of the ulnar groove, and transference of the nerve anterior to the inferior condyle have all been practised with variable degrees of success. We have transferred the nerve in this manner in 15 cases, often with quite remarkable and gratifying results. The object of

the operation is to relieve the nerve of the unusual tension induced by the deformed elbow and to protect it against frequent traumatism. When these factors which bring about the damage to the nerve cease, a degree of restoration is to be expected, such as the permanent changes in the nerve will permit. It is not expedient to resect a pseudoneuroma because of the additional damage which may be produced. In numerous instances the sheath of the nerve has been split over the pseudoneuromas and where constrictions appear, in the hope that this relief of tension may provide better nutritional conditions for the nerve-fibers.

In 1878 Panas reported a similar case. Since then others have described the condition in detail. Sherren in 1908 collected 23 cases from the literature, adding 2 cases from his own practice. He resected the ulnar nerve in 1 case and excised the elbow-joint in the other, with a marked improvement in function in both cases. Hunt in 1916 reported 3 cases, naming the condition "tardy or late paralysis of the ulnar nerve," the term which I have adopted.

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ARTERIOSCLEROSIS OF THE NERVOUS SYSTEM. AN ANALYSIS OF 59 CASES WITH CORD CHANGES

HENRY W. WOLTMAN

ATHEROMATOUS degeneration is not peculiar to old age; it may occur as early as the age of twenty. The change may be diffuse or chiefly limited to an organ, such as the aorta, the peripheral circulation, the heart, or the brain. The cause is said to be toxic. Josués first attempted to produce arteriosclerosis experimentally by administering epinephrin and hydrastin to rabbits. By the use of epinephrin alone I was unable to produce atheromatous changes in vessel walls of rabbits which I was satisfied might not have been there before. Very important may be the work of Saltakow, who believes that he can produce arteriosclerosis by injecting staphylococci. Typhoid organisms have also been used. If the disease can be produced by these organisms it may eventually be added to the already replete list of disorders resulting from focal infections.

I shall not undertake a discussion of the pathologic changes, which have been worked out in great detail, although the correlation with the clinical expression of the condition is not fully understood. The vessel walls are often greatly thickened, particularly the intima, as shown in Fig. 132, which may ulcerate and liberate emboli; the lumen of the vessel may be entirely obliterated. Figure 133 shows one of the anterior cerebral arteries completely closed. This led to marked softening of the part of the brain supplied by this vessel. Atrophy and regressive metamorphosis of senility, with disappearance of the functioning wall elements, and replacement by connective tissue may occur. In this event the vessel becomes very thin and dilated (Fig. 134) and may readily rupture. Miliary aneurysms are not so significant as they were once considered.

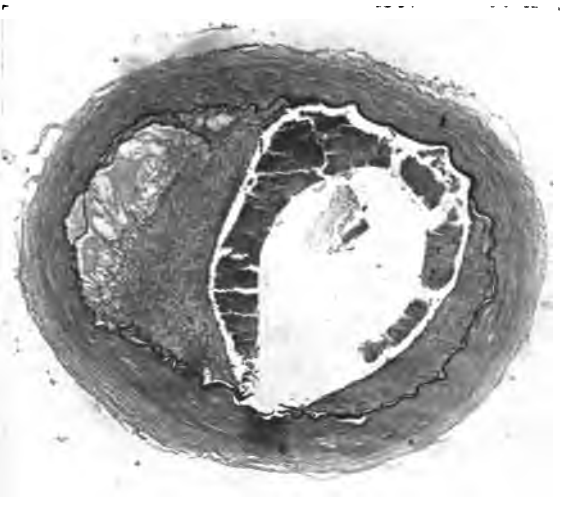

Fig. 132.—(Case 182,690.) Weigert's elastic tissue stain. One of the cerebral vessels showing marked intimal thickening and some splitting of the inner elastic membrane. × 35.

Fig. 133.—(Case 226,169.) Weigert's elastic tissue stain. Complete closure of left frontal cerebral artery. × 30.

Secondary changes take place in the nervous tissue which is poorly nourished; sclerotic areas may be seen throughout the brain and cord surrounding the degenerated vessels. Here and there an area of softening, or malacia, may be discerned. In addition, a parenchymatous disintegration may be found affecting both cells and fibers. Increased deposit of pigment is common, and has been looked on as a cause of death through

Fig. 134.—(Case 68,834.) Hematoxylin and eosin. Cross-section of basilar artery showing marked thinning of the vessel wall. × 25.

interference with cellular metabolism. A more nearly correct interpretation would be to consider it a coincident expression of senescence rather than the cause of it. In the cord a degeneration of tracts in the lateral and posterior funiculi, or a subacute combined sclerosis may result. Occasionally the peripheral nerves take part in the degeneration; however, not nearly so often as in pernicious anemia, a fact well demonstrated by Hamilton and Nixon.

MAYO CLINIC SERIES

Fifty-nine patients (40 per cent.) of the 148 in this series had objective evidence of cord involvement. Inasmuch as these patients showed practically all of the symptoms of the cerebral type as well, and since evidence of cord involvement strengthens the diagnosis, they were selected for a more detailed study. The males predominated, with 64 per cent. (Fig. 135). The age extremes were fifty and seventy-eight years, the average being sixty-three years.

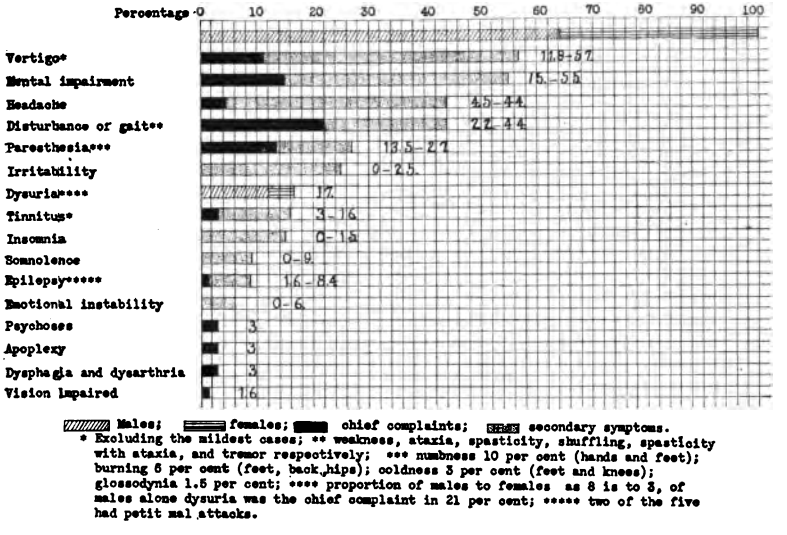

Fig. 135.—Complaints in 59 cases of cerebrospinal arteriosclerosis.

Symptoms.—The chief complaint of 22 per cent. of patients was weakness, but on further inquiry it was noted in 44 per cent. A close analysis of this complaint revealed the fact that in many instances the difficulty was not really weakness, but a difficulty referable to ataxia, spasticity, a combination of the two, and to tremor.

Changes in the mental sphere are common, particularly impairment of memory; this was the chief complaint in 15 per cent. and a minor disturbance in 55 per cent. of cases. A finding of greatest importance in diagnosis is poorly sustained

attention, observed in 62 per cent. It is often of a much greater degree than the patient's general appearance and behavior suggest. Co-operation, particularly in the sensory tests, is poor; the patients either fail to answer or else drop into the habit of giving the same response in a rhythmic manner. Discrimination is impaired and testing vibratory sensibility must often be abandoned. These findings are important from the practical standpoint and the only other disease in which they are observed in so striking a manner is tumor of the frontal lobe. The differentiation, particularly in the absence of choked disks, is sometimes impossible. Arteriosclerotic dementia was present in 3 per cent. Irritability developed in 25 per cent., and some of the patients were brought for examination by relatives for this reason, although none voluntarily gave this as the chief complaint. Contrary to the usual description, the patient often is decidedly less irritable than he was during health. Some emotional instability is frequent, but was marked in only 6 per cent.

Paresthesias are relatively rare in contradistinction to their incidence in pernicious anemia; they occurred as a chief complaint in 13.5 per cent. and as a subsidiary complaint in 27 per cent. Numbness of the hands and feet, burning sensations of the feet, hips, and back, coldness of the feet and knees, the sensation of a needle broken off in the toes, and burning of the tongue (glossodynia) were the principal complaints.

Vertigo was a common and fairly characteristic complaint. Headache was present in some form in 44 per cent. and severe in 4.5 per cent. It was usually of a dull, heavy type, bregmatic or frontal, but sometimes it was stabbing and quite sharply localized.

Strokes, hemiplegic, hemianopic, aphasic, and so forth, are severe and incapacitating symptoms; too much stress, however, is ordinarily laid on these as necessary requisites to a diagnosis of cerebral arteriosclerosis. I shall, therefore, limit my discussion of these.

Tinnitus is fairly common and furnishes valuable corroborative evidence of wide-spread involvement.

Arteriosclerotic epilepsy, differing in no essential respect from idiopathic attacks, is sometimes very distressing. It may occur as petit mal or grand mal in the proportion of 2 to 3. It is interesting how often the patient attributes these attacks to being "overcome by the heat," although the day may have been relatively cool. One man came because of what he considered to be repeated "sun-strokes."

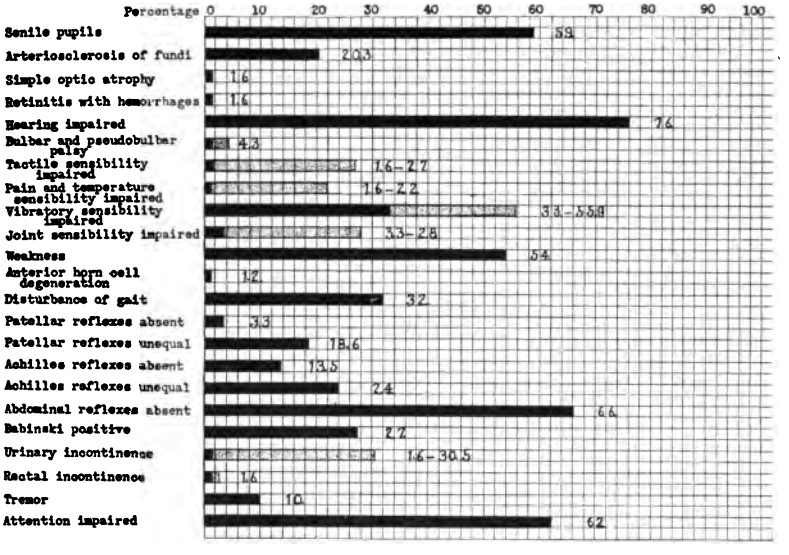

Fig. 136.—Summary of neurologic findings in 59 cases of cerebrospinal arteriosclerosis.

Figure 136 gives a résumé of the objective findings. It indicates very forcibly that the diagnosis does not represent an impression based merely on the general appearance of the patient. Some help is gained from an examination of the pupils. Changes are frequently noted, principally irregularity, and poor reactions to light and accommodation. Since inspection of the pupil is now recognized as an important procedure in the detection of syphilis, the interpretation of pupillary anomalies in aged persons must be made with caution. In no case must examination of the fundus be neglected. Knapp has called attention to the fact that fundi showing arteriosclerosis in every

instance indicate an associated cerebral arteriosclerosis, but the reverse is not always true. Abnormal reflexes are not uncommon, but they are not particularly distinctive. Vibration and joint sensibility are not so much impaired proportionately as is combined sclerosis of pernicious anemia, in 150 cases of which previously reported joint sensibility was impaired in 60 per cent. and vibration sensibility in 82.4 per cent.

An interesting symptom and one of practical application is urinary disturbance from which many of these patients suffer. This constituted the chief complaint in 17 per cent. of all patients, and in 21 per cent. of the men. On further questioning, 28 per cent. of men reported difficulty in starting urine; 30.5 per cent. had some trouble in controlling it; and 1.6 per cent. had complete incontinence. The prostate was examined by rectum in all, and found to be enlarged in but 8 per cent. Cystoscopic examinations were performed when necessary; trabeculated bladder was found in 8 per cent. In 4.5 per cent. the only explanation of the trouble seemed to be cord bladder, which neurologic examination verified; 5 per cent. of the men had trabeculated bladders and benign hypertrophied prostates; in only one of these cases, however, the prostatic obstruction seemed sufficient to account for the trabeculation, and prostatectomy was performed; the improvement justified the procedure. An abstract of one case typifies all the cases:

Case A260,532. Mr. A. K., aged seventy-eight years, examined February 25, 1919, complained of frequency at night, which had begun four years before, compelling him to void two or three times a night. For the first two or three months he had experienced difficulty in starting the stream. For six months his feet had been cold and there had been a smarting sensation over the soles on retiring.

The patient's blood-pressure was 130 systolic and 86 diastolic. The phenolsulphonephthalein output was 80 per cent. in two hours; the urine was normal. The prostate was normal. Cystoscopic examination revealed a trabeculated bladder without obstruction. Neurologic examination revealed senile pupils, bilateral impairment of hearing, diminished power in the legs,

a little more on the left than on the right, some ataxia in walking, slight impairment of sensibility to touch and pain over the feet and buttocks, loss of sensibility to vibration below the thorax, left patellar reflex slightly exaggerated, right slightly diminished, Achilles' reflexes almost absent, abdominal reflexes absent. He had difficulty in controlling the urine, and some incontinence of bowel movement on taking a cathartic. A diagnosis of cerebrospinal arteriosclerosis was made. The cord involvement was obviously marked and could easily explain the dysuria. Prostatectomy would have been futile and disastrous.

The relation between high blood-pressure and cerebrospinal arteriosclerosis appears not to be generally understood. Objec-

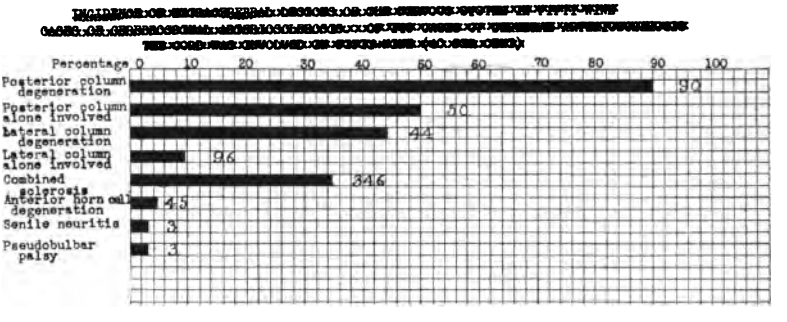

Fig. 137.—Incidence of extracerebral lesions of the nervous system in 59 cases of cerebrospinal arteriosclerosis.

tion to the diagnosis is often raised on the grounds of normal blood-pressure. The fact remains that 64.4 per cent. of the patients have an average pressure of 130 systolic and 78 diastolic. The extreme systolic pressures were 100 and 250, the extreme diastolic, 52 and 140. Doubtless, lack of vessel elasticity is a large factor in explaining the comparatively low pressure. Low blood-pressure is also recorded in other forms of arteriosclerosis, such as peripheral and cardiac.

The Bárány test was performed in many of these cases, but the results were not included in the charts. The test gives us information that can be utilized in formulating a final interpretation of our findings.

The types of cord lesions are shown in Fig. 137. Subacute combined sclerosis was found in 34.6 per cent.

Differential Diagnosis.—Since the neurologic findings alone often suffice for a diagnosis of pernicious anemia, and since the resemblance of these findings to those in arteriosclerosis may be very close, a word may be added regarding the differential diagnosis of these two conditions as it applies to the neurologic picture. The neurologic findings in pernicious anemia have been discussed in detail previously[5, 6]; one of the outstanding symptoms is the persistent paresthesias in the extremities in about 80 per cent. This is observed only rarely in arteriosclerosis, particularly in the hands. Another distinguishing feature is the outstanding impairment of vibratory sensibility over the lower portion of the body in pernicious anemia, while tactile, pain, and temperature sensibilities are often relatively unaffected. Other evidences of general arteriosclerosis, such as retinal arteriosclerosis, aid in distinguishing the two. Differences in the mental reactions are striking and of considerable value from the standpoint of differential diagnosis. It must not be forgotten that the two conditions often exist in the same patient, when it may or may not be possible to differentiate them. Often under these circumstances the neurologic evidence is of secondary importance and can only be utilized in a corroborative way.

CONCLUSION

I do not wish to leave the impression that arteriosclerosis of the brain and spinal cord is an entity that is entirely divorced from changes in other parts of the body. It is simply one expression of a general process and one means of recognizing the general process. Evidence of a similar change in the viscera and in the extremities is often obtainable and may be of equal significance so far as the patient's well-being is concerned.

A word with regard to the prognosis and management of these patients: They are often introspective to the highest degree, and on the slightest occasion develop a distressingly morbid attitude. This is unfortunate, particularly since sometimes it must be attributed to an erroneous impression among

medical men regarding the disorder. While the condition of some patients is most distressing and progresses inevitably, this is exceptional. These patients need, almost more than any others, the assurance that they are not a burden. The will and the desire to live must be reawakened. Correction in habits of living, the institution of a noon-day nap, and the establishment of an interesting daily routine are often followed by surprising improvement. These patients come to us at a most critical period of their lives, and as physicians we owe them every possible consideration and aid that the science and art of medicine can supply.

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CLINIC OF DR. REGINALD FITZ

Case I. Malignant Disease of the Liver and Gall-bladder with Symptoms of Pelvic Disease and Neurasthenia.

Case II. Chronic Dental Infection.

Case III. Exophthalmic Goiter in a Young Woman with a Familial History of Diabetes Mellitus.

TODAY I shall demonstrate 3 cases in order to emphasize the importance of careful history taking and thorough physical examination in ordinary diagnosis and treatment.

CASE I (342,964)

Mrs. W. J. A., a woman aged forty-one years, came to the Mayo Clinic December 6, 1920. She was born in Canada, and had taught music before her marriage. Since then she has led a busy life, attending to her home and children. Her family history is negative for cancer or tuberculosis. She was married twenty years ago and has had three normal pregnancies and one miscarriage, not induced, at two months. Her children are now nineteen, seventeen, and sixteen years of age. Her menstrual history is negative. Menstruation began when she was fifteen years of age and has been regular, painless, and not excessive. Her last period ended one week before she came to the clinic. For several years she has been bothered by a persistent leukorrhea. Her appetite and digestion have been normal. Her bowels move regularly. Until recently she has not been nervous and has slept well. She has always taken a considerable amount of tea and coffee. Her previous health has always been remarkably good. She remembers no illness except her pregnancies and an occasional mild attack of tonsillitis. Her family physician had advised her to have a lacerated cervix and perineum repaired twelve years before. At the time she paid no attention to this advice, as she felt perfectly well.

About two months before her examination, however, she began to lose weight and to be very nervous, so that finally she was even affected "by the electricity of music" and was unable to bear the sound of a victrola. At about that time she noticed a dragging and burning sensation in the lower part of the pelvis and complained of increased frequency of urination. Finally, she consulted her physician for these symptoms and he referred her to the Mayo Clinic.

The patient's history, in brief, therefore, is that of a middle-aged woman who has had a badly lacerated cervix and perineum for many years following three pregnancies and who has worked hard all her life. For two months she complained of the characteristic nervous and physical symptoms which are often met with in hard working women before the menopause and are associated with gynecologic conditions. There is no history of digestive upset. The loss of weight, 19 pounds in the last two months, has been more sudden and rapid than is usually encountered in such cases.

Physical examination showed a well-developed and fairly well-nourished woman who looked a trifle pale and anemic. The teeth showed a moderate pyorrhea, the tonsils were small, but drained fluid pus. Pus also drained from the right middle turbinate bone. The heart and lungs were normal. The systolic blood-pressure was 125 and the diastolic 85. The abdomen was negative except that a smooth edge of the liver, not tender, was felt about 5 cm. below and parallel with the costal margin. There was a bad tear in the perineum, a severe cystocele, a prolapsed and lacerated cervix, and a uterine fundus which was retroverted, but which was freely movable.

Roentgenograms of the sinuses, made on account of the purulent discharge from the right middle turbinate, were negative. Films of the teeth were negative. Roentgenograms of the chest and stomach were not made.

The urine was normal. The Wassermann reaction on the blood was negative. The hemoglobin of the blood was 65 per cent. The erythrocyte count was 3,800,000; the leukocyte count was 8000.

On the whole, routine physical examination revealed that the patient had lost 19 pounds in weight in two months, had a slight secondary anemia, a gynecologic condition which might well be accountable for the anemia, and a smooth non-tender liver such as can often be felt in persons with relaxed abdominal muscles who have recently lost weight.

Obviously the treatment indicated was surgical. Dr. W. J. Mayo saw the patient in consultation and advised a repair operation on the perineum and a suprapubic incision in order to examine the liver. His reason for insisting on exploration of the liver in this case was largely owing to the history of recent and rapid loss of weight in a woman more than forty years of age, with a palpable epigastric tumor.

At operation an enlarged liver and spleen and a gall-bladder containing a number of stones, one of which was obstructing the cystic duct, were found. There was also a tumor, histologically lymphosarcoma, which appeared to originate in the outer edge of the gall-bladder and to grow behind the gall-bladder into the liver. The tumor was not encapsulated and was removed with the gall-bladder (Fig. 138).

The patient made an uneventful immediate recovery, and was treated at once with radium and Roentgen rays. Six and a half months later her physician writes that she has gained 15 pounds in weight and feels perfectly well.

Cancer of the gall-bladder is not excessively rare, being found in about 2 per cent. of all operations on this organ. Sarcoma of the gall-bladder, on the other hand, is most unusual. Magoun and Renshaw, in a recent analysis of cases observed in the Mayo Clinic from January, 1907 to January, 1921, found only this one case. This case is not presented, however, in order to discuss the symptomatology and pathology of malignant disease of the gall-bladder. It serves better to illustrate how easily a clinician may be misled in his diagnosis by symptoms of functional disturbance in the presence of organic disease.

It is a dangerous practice for any physician to make a diagnosis of neurosis in a patient more than forty years of age. At this time of life degenerative changes begin to occur in most

persons. Cerebral or renal sclerosis may produce insidious symptoms which are of an organic cause and which usually are progressive. Syphilis of the nervous system which has been quiescent may become active. Above all, malignant disease must be sought for, especially in patients who have no localizing

Fig. 138.—(Case 342,964.) Lymphosarcoma of the gall-bladder with adjacent hepatic tissue.

signs, but who have lost weight rapidly. The rectum and large intestine must be examined carefully, since early malignant disease in this part of the bowel may be symptomless. Cancer of the stomach without pyloric obstruction may involve almost the entire organ without producing more signs than loss of weight and strength. Finally, as in this case, malignant disease of the

gall-bladder may become advanced before it produces its usual symptoms of pain, jaundice, and cachexia.

CASE II (352,384)

Mr. D. A., an insurance agent, aged fifty-three years, came to the Mayo Clinic March 14, 1921. He was born in this country and has been engaged in active business since he was a young man. He has been married twenty-six years. His wife was never pregnant. His grandmother died of pulmonary tuberculosis, but the patient was not directly exposed to this infection. There is no familial history of cancer. He has enjoyed fairly good health until recently. As a boy he had typhoid fever followed by an indefinite history of gall-bladder trouble without jaundice. Twenty years before consultation he had rheumatic fever. He has had grip several times and two attacks of malaria. He has also had gonorrhea. Until shortly before examination his appetite and digestion had been normal, his bowels regular, and his sleep sound. He has never used alcohol to excess. He smokes moderately and does not drink tea or coffee to excess.

In September, 1920 his teeth were removed on account of "pyorrhea and ulcerated gums." Two months later he developed bronchitis which was not associated with sufficient fever or malaise to drive him to bed, but was severe enough to make him feel ill for a week or ten days. As the attack of bronchitis disappeared his appetite diminished and he began to lose weight and strength. At the time his teeth were extracted he weighed 200 pounds. In the next six months his weight dropped to 173 pounds. During the period of loss of weight he had no fever, cough, nausea, pain, vomiting, or diarrhea. His bowels were costive and became "gassy" when he ate anything solid. He was able to chew his food satisfactorily with a set of false teeth. He had not obviously lost blood, although his friends told him that he had grown pale. He had consulted three physicians, who found no cause for his pallor and loss of weight.

The essential features of this history, therefore, are increasing pallor and loss of weight and strength after an acute respiratory

infection in a middle-aged man who has recently had all his teeth removed, and who in the past had had typhoid fever, rheumatic fever, malaria, and gonorrhea.

Physical examination showed a well-developed man who looked pale and as though he had lost at least the amount of weight stated. His gums were entirely healed and were not tender. His tonsils were moderately enlarged, but did not drain pus. The systolic blood-pressure was 150, the diastolic 80. Examination of the heart, lungs, abdomen, genitals, rectum, nervous system, skin, eye-grounds, and extremities was negative.

Clinical laboratory tests showed normal urine and stool, a negative blood Wassermann reaction, blood containing 69 per cent. of hemoglobin, a red count of 4,000,000, a white count of 7000, and a smear with normal differential count of the leukocytes and with normal appearing erythrocytes. Gastric lavage did not afford evidence of food retention or bleeding. A roentgenogram of the stomach was negative. The gastric acidity was within normal limits.

On the whole, physical and laboratory findings were more nearly negative than might have been predicted from the history. Malignant disease was not found, although it was suspected from the history of progressive loss of weight. There was insufficient evidence for believing that cardiorenal disease could have caused so much prostration without signs in the urine, heart, or eye-grounds. A chronic cholecystitis with or without gall-stones might have caused both the loss of appetite and sensation of intestinal gas, especially as there was an antecedent history of typhoid fever. There was not, however, the least tenderness or spasm over the gall-bladder region and the history was not sufficiently typical of gall-bladder disease to justify an exploratory operation. The blood-count and blood-smear ruled out any primary disease of the blood.

Dr. Bonta saw the patient in consultation and advised a Roentgen examination of the mouth, despite the history that all teeth had been removed six months previously. A copy of a portion of this film is shown in Fig. 139. A root of one tooth had been left at the time of extraction. Around this stump

was an abscess cavity which may have been there for years, or it may have developed following extraction. In any event, the abscess and the root were the only positive physical findings. The patient was advised to have the remains of the tooth extracted and the abscess cleaned up. This was done under local anesthesia one week after he was first seen. Since then he has felt much better, but he continues to have a certain amount of biliousness and indigestion and does not consider himself perfectly well. It is difficult to believe, on this account, that chronic sepsis from a dental abscess was the sole cause of his trouble.

This case is instructive, however. At present there is a tendency throughout the country for physicians to advise their patients to get rid of teeth and tonsils for almost any complaint.

Fig. 139.—(Case 352,384.) Root of tooth and abscess cavity in edentulous jaw.

There is increasing evidence to support the view that foci of infection in the mouth may be of great importance in the development of many systemic diseases. There is, on the other hand, no evidence for believing that the indiscriminate removal of normal teeth and tonsils is good practice. Satisfactory dental films can be made easily. True periapical infection can be recognized and treated. Normal teeth can be separated from pathologic teeth and should not be sacrificed. Examination of the tonsils is more difficult, because, although the tonsils may be seen and felt, the gradations from the normal to the pathologic are indefinite, and wide experience is necessary in order to state whether a certain tonsil can reasonably be expected to influence a diseased focus in some remote part of the body. At least, in a given case, it is logical for the internist to insist on

roentgenograms of all teeth which are suspected of being diseased, and on demonstration by the throat specialist of why he considers a pair of tonsils, before removal, a source of systemic infection.

Finally, this case emphasizes the fact that the removal of teeth may be a serious operation. If diseased teeth are cleanly removed there are usually no significant postoperative complications. If, however, the operation is not perfectly performed it results in no benefit and may even do harm. It is, therefore, of practical importance to check up all operations for removal of teeth by postoperative roentgenograms. The same argument is true in the case of tonsillectomy. Unless the tonsil is cleanly removed and no tonsillar remnant is left the operation is unsuccessful and often has to be done over. These patients, therefore, must be examined after such procedures in order to make sure that the desired results have been accomplished.

CASE III (354,364)

Miss McB., aged twenty years, came to the Mayo Clinic April 4, 1921. She was born in this country and has been attending school. Her father and mother, one brother, and two sisters are well. One brother died of diabetes when ten years of age, and one sister died of diabetes when twenty-three years of age. There is no familial history of cancer or tuberculosis. Menstruation began when she was twelve, has been regular, painless, and not excessive. Her appetite and digestion have been normal, her bowels have moved regularly, she has slept well, and led a normal life for a girl of her age. She drinks one cup of coffee a day. She has had mumps and whooping-cough, but no other diseases of childhood. She had been perfectly well, as far as she knew, until four weeks before consultation; then, while at school, she "felt a little sick," with a sensation of pain in her bones and joints, and with a feeling of general malaise. She does not know whether she was feverish at this time. She seemed to improve and was able to return to school, although she still became easily tired, perspired easily, was nervous, and, according to her mother's statement, did not look well. Her

mother became worried and had a specimen of the patient's urine examined. It was reported to contain a trace of sugar. On this account she came to the Mayo Clinic for a more detailed study. The girl normally weighed 106 pounds. She had lost 5 pounds in about four weeks.

In summary, therefore, the history of this case is that of a young girl who has had a brother and sister who had died of diabetes early in life. She herself was well until a month before examination, when she probably developed an acute infection of undetermined etiology. Since then she had tired easily, was nervous, and had lost 5 pounds in weight. One urinalysis is said to have contained a trace of sugar.

Physical examination showed a well-developed and fairly well-nourished girl with prominent eyes, but without notable exophthalmos. Her teeth were in good condition. Her tonsils were moderately enlarged and drained pus. She had a palpable thyroid gland over which could be felt a thrill on the right and left sides. On auscultation a bruit was heard over the entire gland. The heart was negative. The pulse-rate was 120. The systolic blood-pressure was 130, the diastolic was 75. There was a fine and coarse tremor of the hands and tongue. The knee-jerks were exaggerated. The skin perspired easily. Examination of blood showed that the patient was not anemic. Two specimens of urine were normal, except that the sediment on one examination contained a rare cast. Neither specimen contained sugar. A roentgenogram of the chest was normal.

As a result of the history and of these findings the patient was sent to the hospital to be studied further under circumstances which could be controlled. She was given a diet containing 250 gm. of carbohydrate, 60 gm. of protein, and 60 gm. of fat. While on this diet her urine contained a faint trace of sugar, although her blood-sugar in the morning before breakfast was 0.10 per cent. Her basal metabolic rate was 34 per cent. above normal.

On the whole, physical examination showed a young girl in good condition, with septic tonsils, tachycardia, tremor, and a

palpable thyroid gland over which could be felt a thrill. Her basal metabolic rate was above normal, supporting the impression that the patient had exophthalmic goiter. Her sugar tolerance was diminished; on the other hand, her fasting blood-sugar concentration was within normal limits.

The patient developed acute tonsillitis while in the hospital and was sent home to convalesce. She came under observation again two weeks later, feeling and looking well, but with a metabolic rate 45 per cent. above normal. Her urine was sugar free. It was decided to remove the tonsils despite the increased metabolism in the belief that the septic tonsils might be harmful not only for the exophthalmic goiter but also for any latent diabetes. The operation was successfully performed under local anesthesia.

Three weeks later the patient returned for a third examination, having rested quietly at home in the interim. Her tremor and nervousness were more marked. Her systolic blood-pressure was 142, her diastolic 60, and her basal metabolic rate had increased to 58 per cent. above normal. The urine continued to remain free from sugar.

Dr. Pemberton saw the patient in consultation; in view of the fact that the patient was in excellent condition and was not improving at home he advised thyroïdectomy. Accordingly, May 26th, about ten weeks after the symptoms were first noted, Dr. Pemberton injected 4 c.c. of boiling water into the left lobe of the thyroid gland. This was not followed by any reaction. Five days later he removed about three-quarters of the gland under gas-oxygen anesthesia, finding each lobe enlarged to about twice its normal size. The patient made an uneventful recovery from the operation. Six weeks later she reported by letter that she felt perfectly well, had gained 14 pounds in weight, and that her urine had not contained any sugar since she had left the hospital.

This case is interesting from the point of view of diabetes. In the first place the fact that the patient had a family history of diabetes is important. Diabetes undoubtedly tends to appear in certain families. In my experience a more severe

type of diabetes develops in the second generation of diabetic families than in the first. Joslin and Riesman, however, have recorded a mild type of the disease occurring in younger brothers and sisters of the same family, the older members of which have had severe diabetes. In any event, the mother of this patient has been properly trained. Knowing that her children may develop diabetes she is constantly on her guard for the manifestations of the disease in her family and had her daughter's urine examined as soon as she was ill. This is the proper attitude to instil in the minds of mothers of diabetic children. Repeated urinalyses of all members of the family should be made at intervals, so that if diabetes develops it can be brought under control with the least possible loss of time.

The coincidence between thyroid disease and diabetes in the same family is also interesting. Such a coincidence has been noted before. Some authors claim a "thyroid diabetes" which improves or becomes cured when the diseased thyroid gland is removed. At present, it seems to me, the exact relationship between hyperthyroidism and diabetes is not clear. The two conditions occur together in a certain proportion of cases. Exophthalmic goiter and diabetes do not apparently make a fortunate combination. In these cases, usually, no matter how well treated is the goiter, the diabetes runs an acute and rapidly fatal course. In cases of toxic adenomas and diabetes, on the other hand, the removal of the adenomas and lowering of the metabolic rate often result in great improvement of the diabetes.

The low sugar tolerance which is frequently seen in exophthalmic goiter does not mean that the patient is necessarily prediabetic, even if he has a diabetic-like curve of glycemia following the ingestion of 100 gm. of pure glucose. In fact, the Mayo Clinic records show that while almost 2 per cent. of the patients with exophthalmic goiter have traces of sugar in the urine from time to time or have a lowered glucose tolerance, as estimated by the alimentary test, the subsequent development of a true diabetes, so far as is known, is much less frequent. It is impossible to know now whether or not Miss McB. is diabetic. On

account of her family history, however, the immediate indications for treatment are plain. She should rest for a time sufficient to recover from all the effects of the goiter operation. She should be taught the simple rules of dietetics and should not be allowed cake, candy, ice-cream, rich desserts, or an excess of starchy foods. She should not be allowed to gain weight rapidly. Her present height is 5 feet, 5 inches and her weight 115 pounds. For her age and height she should weigh 128 pounds and can thus afford to gain a little. It will be safer for her, however, to gain weight slowly and to remain underweight rather than to become stout. Her urine must be examined once a month. She must be taught to collect a twenty-four-hour specimen rather than a single one, and must have it tested by the family physician rather than by herself. On the whole, she must be considered a diabetic suspect. If sugar reappears in the urine she must undergo strict diabetic treatment immediately because of her family history and because of the grave prognosis in exophthalmic goiter and diabetes. If she has a recurrence of her goiter symptoms she must report to her physician as soon as possible.

CONCLUSIONS

I have demonstrated these 3 cases to illustrate certain simple clinical facts which are well known to all physicians, but which do not lose force by repetition. A systematic history and physical examination is the only basis for proper diagnosis and treatment. It is dangerous to make a diagnosis of neurosis in any patient more than forty years of age. Rapid loss of weight in the absence of definite physical signs or history is always significant. Normal teeth and tonsils must not be sacrificed. If diseased teeth and tonsils are removed they must be removed perfectly or else the operation is almost valueless. The early diagnosis of diabetes mellitus is sometimes difficult. The urine of children in diabetic families should be watched closely with a view to preventing the disease before it develops, rather than treating it when it is too late to accomplish a cure.

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HYPERSENSITIVITY TO FOOD PROTEINS

ARTHUR H. SANFORD

DURING the last few years increasing interest has been manifested in the attempt to demonstrate protein sensitization as an etiologic factor in bronchial asthma. The painstaking studies of Walker and his associates have given us a criterion for efforts in this line of clinical investigation. The fact also that recently many proteins carefully prepared for diagnostic tests have been placed on the market has made diagnosis by means of skin reactions an easy procedure. We have followed this line of clinical laboratory diagnosis for a number of years with enough positive findings to make us feel that there is something worth while in this method.

In one year about 225 patients with bronchial asthma come to the Mayo Clinic. The proportion of positive skin reactions that seem significant to the number tested is only about 1 in 4. Pollen sensitization characterizes by far the greater number of significant positive skin reactions. Occasionally, however, an asthmatic patient is found who shows by means of this test positive reaction to some of the very common foods, elimination of which from the diet seems to prove by symptomatic improvement that it is the true etiologic factor. In about 20 histories of positive skin tests with food proteins a few cases have been selected for discussion. Although the cases present nothing especially new, they may be of interest since they are confirmatory of theories advanced by other investigators in reporting similar cases.

CASE HISTORIES

Case I (87,980), Mr. F. P., aged thirty-three years, now in the shoe business and formerly a sheet and metal worker, came to the Clinic first in 1913, complaining of loss of strength, indigestion, nausea, vomiting, and diarrhea for about two years.

His appetite was good, he ate anything, but had considerable epigastric distress after eating.

The patient returned to the Clinic in 1916, reporting that his gastric symptoms had improved considerably during the three years. His chief complaint at this second visit was asthma; he had had his first attack one month before coming to the clinic. It came on during the day about noon; dyspnea was quite pronounced and lasted about twelve hours. He did not cough with the first attack. He had the second attack in the morning two or three weeks later; a persistent cough, most marked at night, followed. He also gave a history at that time of having had "hives" since infancy. It came on when he was cold, tired, chilled, or had indigestion. His general health was fair, his appetite was good, his bowels were regular. He had no other complaint, except at times nocturia, which may have been accounted for by a slight enlargement of the prostate which was found on examination. Only bronchial thickening was found by Roentgen-ray examination. The urinalysis was negative. The nose and throat examination revealed a moderate degree of tonsillar hypertrophy; tonsillectomy and local treatment for the asthma were advised. The tonsillectomy was not performed, however, at this time.

April 3, 1917 the patient again visited the Clinic. He stated that he had not had asthmatic attacks since he had had a nasal treatment two weeks before. He still had a loose cough, with considerable expectoration. There were no night-sweats and no fever. His appetite was good, and he was feeling well in every way aside from his bronchial spasms. During the winter he had had an eruption between the fingers which was worse during March, with considerable itching, spreading on the wrists and somewhat on the neck. He visited the Clinic a number of times for local treatments of the nose and throat which apparently relieved the asthma.

April 16, 1918 the patient's chronically infected tonsils were removed; there is no record that this operation caused relief of his asthmatic trouble which he was having fairly constantly. Soon after this skin tests were performed. He was found to be

sensitive to wheat and eggs, and was advised to omit these articles from his diet, but not much attention was paid to the findings at this time.

March 24, 1921, as the patient had had considerable trouble from asthma during the winter, he again came to the Clinic and skin sensitization tests were made with a number of substances. He was negative to bean, salmon, oyster, onion, corn, potato, timothy, sweet potato, beef, cabbage, *Streptococcus hemolyticus*, *Streptococcus non-hemolyticus*, *Diplococcus pneumoniæ* (Type II), *Staphylococcus albus*, *Streptococcus viridans*, pork, cheese, ragweed, and goldenrod. He was positive to a slight extent to rye, and markedly positive to tomato, whole egg, wheat proteose, oats, and barley (Fig. 140). At this time he was placed on a strict diet, with eggs and wheat and tomatoes omitted from his daily bill of fare, with the result that he did not have an attack of asthma until June 30, 1921, when on a warm summer evening while he was mowing the lawn he had a slight attack. It was suspected that he might also be sensitive to some pollen, and he was tested to a number of the pollens of the flowers and grasses that were in flower at this time. He was positive to the clovers, chiefly alfalfa, red clover, and sweet clover. This may be somewhat significant as there was an abundance of clover on the lawn on which he had been working. The patient is now being treated in an attempt to desensitize him to wheat by giving minute doses of whole ground wheat placed in capsules. The dosage began with 0.02 gm. three times a day, which was increased after three days to 0.04 gm. three times a day. This dose will be increased rapidly as the patient's tolerance seems to be established. At present he is not having attacks of asthma.

Case II (185,923), Mrs. S. A. M., a housewife, aged thirty-one years, first came to the Clinic February 16, 1917, complaining of frequent colds and sore throat and of asthmatic attacks since childhood.

Nose and throat examination revealed a deflected septum, polypoid turbinates, enlarged tonsils, and a mucoid discharge from the nostrils. Adenoidectomy had been performed elsewhere four years before.

Tonsillectomy was recommended and performed March 17, 1917.

The patient returned to the Clinic September 15, 1919. At that time the nose and throat examination revealed that the tonsils had been cleanly removed, although the patient was complaining of more throat trouble than ever. She had a great deal of headache, and what she considered repeated attacks of cold. Skin sensitization tests showed that the patient was markedly positive to wheat, oats, rye, barley, wheat proteose, and slightly positive to pea, and was negative to egg-white, beef, tomato, lettuce, squash, horse dander, rice, salmon, bean, potato, milk, strawberry, cabbage, and to the pollens of goldenrod, red top, oat, orchard grass, corn, ragweed, and timothy. The suggestion was made that the patient abstain from all wheat in her diet and also avoid handling wheat flour. She has followed this advice for nearly two years and is free from trouble when she carries out this régime. At present we are attempting to desensitize her to wheat by means of feeding ground whole wheat in capsules.

Case III (353,822), Mrs. B. B., a housewife, aged thirty-six years, came to the Clinic March 29, 1921, complaining chiefly of bronchial asthma. Her mother has autumnal hay-fever and asthma; otherwise the family history is negative. Since girlhood the patient had had frequent colds, no worse one time of the year than another, but at intervals she had had sneezing attacks two or three times daily. She had had severe attacks of bronchitis in 1905, 1913, and 1916. During these attacks she could not lie down. Since then she had had frequent attacks of asthma, usually nocturnal. They may recur daily for two weeks, then disappear for two weeks. The attacks are very severe and not limited to any particular time of the year.

At the time of the examination the examining physician noted that the bronchial asthma seemed to be of the anaphylactic type, that there was no history of urticaria, but that the source is probably bacteria or food proteins. Skin sensitization tests were carried out March 29 and 30, 1921. March 29, 1921, *Micrococcus catarrhalis* and cheese were very positive (++++);

cow's milk, rice, and buckwheat were positive (+++). The patient was negative to *Diplococcus pneumoniæ* (Type III), *Bacillus diphtheriæ*, *Streptococcus hemolyticus*, *Micrococcus tetragenus*, *Streptococcus non-hemolyticus*, *Streptococcus viridans*, *Staphylococcus albus*, chicken feathers, cocoa, corn, whole egg, beef, coffee, chicken, grape-fruit, oat, barley, and potato. The patient was further tested the next day, March 30, 1921, with other proteins, and was found to be somewhat positive to wheat proteose, whole wheat, and lettuce, markedly positive to tomato and lactalbumin, and negative to the proteins of cabbage, sweet potato, peanut, rye, pork, English walnut, bean, timothy, asparagus, casein, carrot, celery, orange, bluefish, strawberry, oyster, clam, cantaloupe, mustard, plum, rhubarb, and onion. The patient had had one of her worst asthmatic attacks from eating tomatoes; she was on a milk diet, with the idea that it would relieve her asthma. It was thought that she had chronic bronchitis and hypersensitiveness to milk and tomato, and perhaps, to a less extent, to wheat, and it was advised that these foods be left out of her diet.

We have recently heard from this patient. She states that she has rigidly abstained from the foods which seem to cause her trouble and is greatly improved. Her improvement may be due partly to the fact that she does not suffer so much at this time from chronic bronchitis.

Case IV (358,219), Mrs. C. Z., a housewife, aged thirty-eight years, had had bronchial asthma for ten years before examination in the Clinic, May 16, 1921. It first appeared following a severe cold. Since that time during the months of August, September, and October she had had attacks of hay-fever and coryza with respiratory difficulty. These attacks gradually became worse, so that she was bothered every time she caught cold, which was very frequently. Last year she had asthmatic attacks at intervals lasting three or four days, and relieved by morphin. These attacks came on every two to three weeks. Epinephrin gave some relief. She tried vaccine treatment, but noticed no benefit. She believed that goldenrod, golden glow, ragweed, and poppy brought on her attacks, also dust. She

knew of no foods that distressed her. Whenever she went near rabbits or chickens she noticed an irritation in her nose and began to sneeze. She had had so-called bilious attacks all her life and her asthma was worse when she was in this condition. August, 1920 she had an attack of chills and fever with soreness over the right costal margin. There was no real pain. The stools were light colored at that time.

The physical examination revealed nothing abnormal. The nose and throat examination revealed slightly hypertrophied, non-septic tonsils, a boggy membrane in the nose, and nasal polyps. An operation on the ethmoids was performed May 19, 1921. Hyperplastic middle turbinate ethmoid cells containing polypi were removed. Care was taken to clean up as many shreds as possible. A large antrum window was taken down and a large amount of thick pus was encountered.

May 17, 1921 the patient was tested by means of skin sensitization tests and was found to be negative to orange, oat, English walnut, timothy, whole egg, onion, wheat, strawberry, tomato, celery, beef, cheese, casein, pork, goldenrod, daisy, clover, red top, orchard grass, horse-serum, chicken feather, cattle hair, rabbit hair, cat hair, sheep wool, *Bacillus diphtheriæ*, *Micrococcus catarrhalis*, *Staphylococcus pyogenes albus*, *Streptococcus non-hemolyticus*, *Diplococcus pneumoniæ* (Type I), *Streptococcus viridans*, *Streptococcus hemolyticus*, and *Diplococcus pneumoniæ* (Type III). She was markedly positive to the proteins of barley, corn, and potato, and to a less extent to those of buckwheat, chicken, and bean, and slightly positive to rye and wheat. She was also markedly positive to the pollens of ragweed, and to a less extent to rose. There were also somewhat doubtful reactions to the pollens of dandelion and cocklebur. The patient was advised to leave barley, corn, chicken, and potato out of her diet, to eat sparingly of wheat foods unless they were thoroughly well baked or toasted, and to have several preseasonal courses of treatment with ragweed pollen extract.

Case V (356,692), Mr. C. G., aged thirty-seven years, whose occupation is cream testing, came to the Clinic April 20, 1921. The patient's previous personal and family histories were nega-

tive. His chief complaint was asthma. The patient had had grippe in 1891 and soon afterward began having asthmatic attacks, which persisted. He was always worse at night and there was a large amount of non-offensive sputum.

Examinations for *Bacillus tuberculosis* were negative. The patient stated that he could not stand being around dust, hay, or horses. Cabbage and beans seemed to make his attacks worse. April 30, 1921 skin sensitization tests were given. He was negative to horse dander, chicken feather, horse-serum, cattle hair, sheep wool, cabbage, casein, bean, cheese, lactalbumin, timothy, rye, wheat, potato, orange, ragweed, and goldenrod. He was markedly positive to the proteins of oat and tomato, and moderately positive to those of celery and barley. The patient then stated that he was very fond of tomatoes and celery and ate oatmeal every morning. He also used food flavored with celery seed. Although emphysema and chronic bronchitis were far advanced, he was advised to leave these foods out of his diet. A letter from this patient dated July 6, 1921 stated that he is feeling quite well and is free from asthma since he has omitted tomatoes, celery, and oats from his diet.

Case VI (350,959), Mr. E. L. A., aged thirty-three years, a baker, was examined in the Clinic March 1, 1921. The patient's family history was negative. His mother died at the age of thirty-eight years of pneumonia; she never had had asthma. The patient's previous personal history was negative except for various fractured bones. Tonsillectomy had been performed in 1917, and an appendectomy in 1919. He had had attacks of sneezing during which he sneezed daily for a period of one or two months. The attacks were followed by a sense of pressure in the nose and difficulty in breathing. He stated that the trouble was definitely worse after eating heavily, and was aggravated also by catching cold. It usually came on about forty-five minutes after a meal. He never became actually asthmatic, although he had some difficulty in breathing. The patient's eyes were red and he complained of an itching sensation. His nose was red and irritated, and a watery secretion

was very profuse. He used eighteen to thirty handkerchiefs in a week. These spells might come on suddenly at any time of the day.

It was suspected that his occupation might have something to do with the trouble, and skin sensitization tests were suggested. He was negative to barley, oyster, buckwheat, bluefish, rye, clam, oat, corn, rice, and goldenrod, and he was positive to whole wheat, and markedly positive to wheat proteose. In view of this finding it was thought that this patient's vasomotor rhinitis could be attributed to the wheat proteose with which he was daily in contact in his business.

DISCUSSION

The type of asthma from which these patients suffer is often spoken of as anaphylactic. Melzer's classical paper in 1910 on bronchial asthma as a phenomenon of anaphylaxis did much to establish this idea. The similarity of the stenosis of the bronchioles in anaphylactic shock and in so-called nervous asthma, and the immediate relief that is obtained in both conditions from antispasmodics, such as epinephrin, makes the analogy very striking.

Talbot has reported extensively on this condition in children, and speaks of the phenomenon as anaphylactic in cases in which definite sensitivity to food proteins can be demonstrated. In a very extensive paper, with Worthen, Schloss reports their investigation of the permeability of the gastro-enteric tract of infants to undigested protein. It was shown by precipitin and anaphylactic tests applied to urine that the intestinal tract of normal infants is impermeable to undigested foreign protein. However, when gastro-intestinal disturbances are present proteins may be absorbed in an undigested or partially digested state and appear in the urine. The precipitin test applied to the urine for the detection of egg protein is apparently more delicate than anaphylactic tests. These results demonstrate the possibility that certain nutritional disorders may be due to the biologic character of the food. Such a theory may easily account for the acquired hypersensitiveness to any of the foreign proteins.

While the term "anaphylaxis" may be used synonymously with "hypersensitiveness" by some physicians, asthma, urticaria, angioneurotic edema, etc., are spoken of by others, more properly perhaps as "allergic" phenomena. Schloss in 1912 spoke of one case of food idiosyncrasy in a boy of eight years as one of allergy to common foods. This child was not asthmatic, but had an idiosyncrasy for egg, almond, and oatmeal, which might have been acquired by becoming sensitized to these specific foods the first time they were ingested.

Coca, in a discussion of anaphylaxis and allergy, recently proposed the following definitions for true hypersensitiveness:

"Anaphylaxis is an experimental, or induced, non-inheritable hypersensitiveness due to the presence of specific antibodies in certain tissues.

"Allergy is a natural inherited condition of hypersensitiveness which affects only human beings and is not dependent in any way on immunologic antibodies."

Scheppegrell, who has added much to our knowledge of pollen sensitization in hay-fever and asthma, defines allergy in hay-fever and asthma as that form of hypersensitivity due to the inhalation of pollen protein that is congenital, and anaphylaxis as sensitization of an allergic subject resulting from exposure to pollen protein in excess of his inherited resistance. The congenital tendency to these various idiosyncrasies both with regard to pollen sensitization and hypersensitiveness to various food proteins have been mentioned by numerous authors. Adkinson has pointed out the hereditary characteristics of bronchial asthma in the group studied with Walker[16]; she also refers to Cook's large series. Hutchinson in 1886, in speaking of a case of egg poisoning that he had seen in 1883 in which there were no asthmatic symptoms, and in which the chief symptom was gastro-intestinal distress, states that the patient was a young married woman whose sister had the same peculiarity. Orton, in 1886, also mentions a case very similar to Hutchinson's with a history of the grandmother and mother of the patient being unable to eat eggs. If the condition is truly hereditary, Coca's definition of allergy would be pertinent. If, however,

the hypersensitiveness is acquired through the passing of unaltered protein through a permeable gastro-intestinal tract, as suggested by Schloss and Worthen, the asthma might be spoken of as being an anaphylactic phenomenon.

Hypersensitiveness to proteins is readily demonstrated by another allergic phenomenon that is commonly spoken of as "the skin sensitization test." von Pirquet's well-known test with tuberculin "O. T." is, of course, the basis for all tests of this kind. The technic of the test is exceedingly simple. A linear incision is made just through the epidermis, a drop of tenth-normal solution of sodium hydroxid is placed on this incision, and the dried protein is transferred with a wooden applicator to this drop of sodium hydroxid and dissolved therein. The control, on which nothing but tenth-normal sodium hydroxid is placed, is used on every patient, as some skins are so sensitive that they react even to this weak alkali. If the control shows a positive reaction of course the test is of little or no value. Figure 140, which shows the reaction in Case I, demonstrates the appearance of the wheals which manifest themselves usually in from ten to twenty minutes.

We have often noticed that an individual who is markedly sensitive to one or two proteins of foods or of pollens, will show slight reactions to various other substances which may or may not be closely related (Case IV). An interpretation of this condition may suggest that these patients are hypersensitive to a number of different substances, but that contact with only a few of these causes active symptoms, although at some future time trouble may arise from the other proteins. But a more likely explanation is that with a sensitive skin non-specific reactions may occur with substances that may be remotely related to the proteins that are the chief offenders.

Longcope's Harvey lecture on man's susceptibility to foreign proteins should be read by all interested in this subject. This contains a complete review of the literature in connection with the theories that apply to hypersensitiveness.

Rackemann has also reported on a large series of cases of bronchial asthma in the Massachusetts General Hospital. He

classified this disease into extrinsic and intrinsic asthma, and concluded that 28 per cent. of 150 cases were from extrinsic causes. He also emphasized the hereditary character in the extrinsic cases in this type of asthma; 58.7 per cent. showed a history in the immediate family of asthma, hay-fever, or food poisoning,

Fig. 140.—Cutaneous reaction in protein sensitization.

while in the intrinsic poisoning only 10.5 per cent. gave this history.

TREATMENT

There is very little to be said with regard to treatment. Rosenbloom has reported a case that showed the relation between occupation and bronchial asthma. The patient was a baker who was sensitive to wheat and wheat globulin, somewhat

similar to one of our patients (Case IV), except that he was a true asthmatic, while our patient had only vasomotor rhinitis. He discussed treatment under three points: (1) eliminating proximity to the offending substance; in other words, change of occupation and efforts to keep away from all wheat, eating wheat foods, and handling flour; (2) altering the protein by high temperature (some patients are able to eat well-toasted bread, but cannot eat pastry or fresh bread); and (3) desensitizing the patient by feeding small doses of protein.

This last method seems to be the only method that produces results. Hypodermic injections of solutions of protein are of little avail. In 1908, Schofield had a remarkable case of egg poisoning in a boy thirteen years of age, who was desensitized by means of feeding very minute quantities of raw egg beginning first with 1 : 10,000 part of an egg given in a capsule with 2 gm. of calcium lactate. This was gradually increased until in seven or eight months' time the patient was completely desensitized so that he could eat eggs without producing any symptoms. Schloss[11] desensitized a boy eight years of age in a similar manner, using the specific protein ovomucoid. This was fed in capsules three times a day. The doses were gradually increased until the boy was completely desensitized in less than five months' time; at the same time he lost his idiosyncrasy toward almonds and oatmeal. Schloss reported in 1919 further investigations in his desensitization of food idiosyncrasy in 8 infants in which he determined the occurrence and duration of symptoms after the development of toxic symptoms. These observations extended over a period of from two to six and a half years. The patients developed urticaria from one to three hours after the egg was ingested, with no other symptoms as a rule. Desensitization always occurred after the development of toxic symptoms. This lasted for from thirty-three to forty-five days. The period varied in different individuals, but was usually the same. During this time egg-white could be ingested without harmful effect and the cutaneous test to egg protein was negative. The cutaneous test to egg protein and the development of toxic symptoms after the ingestion of egg-white were in close accord. The return of

sensitiveness was usually abrupt. For example, on one day the test might be negative and the patient could eat egg without harm; forty-eight hours later the test might be positive and the ingestion of egg-white cause severe urticaria. One patient became immune at the end of one and a half years, and one at the end of two years. Three of the remaining 6 patients were desensitized by feeding with large amounts of egg protein.

Our 6 cases of food idiosyncrasy reviewed with several others that we had observed previously have been handled chiefly from the standpoint of eliminating the offending protein from the diet. However, as indicated in the clinical notes, 2 patients (Cases I and II) are now being fed with ground whole wheat in capsules of gradually increasing doses, with the hope that we may be able to desensitize them to this very common food. A search of the literature reveals nothing very encouraging in the treatment of this particular type of patient, as by far the larger number of instances of idiosyncrasy to foods have been reported with eggs, and most of the cases of successful desensitization have been with this animal protein. It is, of course, very desirable, however, to enable a person to eat wheat foods if this can be accomplished.

In conclusion I wish to state, as has been emphasized by all other writers on this subject, that no case of bronchial asthma that has occurred before the fortieth year, especially if the dyspnea is of the expiratory type, can be considered to have been studied completely until an attempt has been made by means of skin sensitization tests to demonstrate proteins of some sort as the etiologic factor. If the patient does not give a history of seasonal attacks of asthma, accompanied possibly with hay-fever, or if contact with animals does not seem to be part of the story, and skin tests with the protein of animal emanations are negative, or, if the history is not that of repeated respiratory tract infection and skin tests to the most common bacterial proteins are negative, common food proteins must be suspected of being responsible for the condition, and a careful study of the history of the patient coupled with a judicious selection of those proteins for tests may reveal the cause.

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[1] Walker and his colleagues have made nineteen previous studies, references to which will be found in this article.

ECHINOCOCCUS DISEASE: ETIOLOGY AND LABORATORY AIDS TO DIAGNOSIS[1]

THOMAS BYRD MAGATH

THE diseases caused by animal parasites, like diseases caused by bacteria, spread with the lines of commerce. One notices in reviewing the parasitic diseases occurring in North America that they have become prevalent as new lines of commerce have been opened and immigration from certain parts of the world has increased. Thus there are already on the Western Coast cases of schistosomiasis as a result of oriental immigration to the United States of America. Several cases have been reported of infection by dermatobia, all of which have been imported from South America or Mexico. Many other parasitic diseases in the United States, such as the endemic filariasis of Charleston, S. C., can be traced to definite sources from some foreign country. Echinococcus or hydatid disease has been reported from America for many years. The earliest case I can find was reported in 1819, and since then 309 cases have been reported, which, together with the 25 from the Mayo Clinic reported in this paper, make 334. As yet the United States has not attracted a great number of immigrants from the countries in which echinococcus disease is most prevalent. However, with the attempt on the part of federal authorities, societies, and institutions to induce more persons from South America to come to this country, it is likely that we shall see more cases of echinococcus.

Echinococcus disease has been known since the earliest times of medicine, like many other of the present-day diseases. Thus Hippocrates recognized the condition and recognized it as a cause of death: "When the liver is filled with water and bursts

[1] Presented before the Southern Minnesota Medical Association, Winona, June, 1921.

into the epiploön, in this case the belly is filled with water and the patient dies." Galen evidently was quite familiar with the condition, and Arætæs wrote concerning it at length. The parasite causing the disease was rather thoroughly studied years ago by many men, including such parasitologists as Goeze, Van Beneden, Leuckart, Davaine, and Cobbold. The term "echinococcus" was first used by Rudolphi, being derived from the Greek ἐχῖνος, meaning a hedgehog, and κόκος, a berry. Hydatid means a vesicle, and was first used in reference to the daughter-cysts which to the naked eye appear as little bladders filled with a turbid fluid.

MORPHOLOGY AND LIFE-HISTORY OF THE PARASITE

From the clinical side the disease has been thoroughly studied by Virchow, Luschka, and more recently Blanchard, Vegas and Cranwell, and others. The cause is the infestation of the host by the larval form of *Tænia echinococcus*, a cestode, or tapeworm. This tapeworm, as an adult, lives in the intestine of the dog, jackal, and wolf. It has been found rarely in the domestic cat. It belongs to the general type of cestodes, represented by *Tænia solium* and *Tænia saginata*, but is unlike these forms in that the segments are very small and few in number. Typically the parasite has a head and three segments, giving it a total length of from 2.5 to 6 mm. and a breadth of 0.5 mm. The head is 0.3 mm. in breadth and has a double row of from twenty-eight to fifty hooklets on the rostellum. The hooklets are quite characteristic and diagnostic of the parasite. The head further contains four suckers, each with a diameter of 0.13 mm., which look very much like the suckers of the ordinary tapeworms. The life-history of the parasite is of interest and of paramount importance because the disease can be controlled only through an understanding of its life-history. The eggs which the adult tapeworm lays in the intestinal lumen of the dog are almost globular and about 30 microns in diameter. These pass out with the feces of the dog, undergoing some development in the external world, and are then transmitted to the intermediate host either in the drinking-water or in uncooked

vegetables or other food, or in certain cases may be directly transmitted to human beings who fondle or kiss pet dogs or allow them to lick their hands or face, or the dishes from which they eat. The intermediate host may be anyone of some twenty-seven species of mammals, which include cattle, sheep, pigs, deer, goats, horses, donkeys, rabbits, kangaroos, camels, giraffes, and man; or indeed, one dog may serve both as the final and the intermediary host. von Siebold was the first to rear *Tænia echinococcus* in the dog by feeding it with hydatids removed from cattle. Thomas, Naunyn, and others have succeeded in raising *Tænia echinococcus* from the bladder worm cysts of man, and Leuckart infected young pigs by feeding them with mature segments.

Just how the larval form finds its way into the organ it infects is not clear. However, it seems evident that the larva hatched in the intestine of the intermediary host either gains access to the blood-stream and is transmitted in this fashion to an organ, or it migrates up the common bile-duct, coming to rest in the liver. In any event, the liver is by far the organ most commonly infected; migration may take place through the portal vein. Dévé has been able to produce metastatic hydatid cysts in the brain of a rabbit by injecting the carotid artery with scolices, so that it seems possible that the parasite is capable of being transmitted by the blood-stream. The dog becomes infected by eating infected organs, usually those of sheep or cattle; the larvæ which are contained in the hydatid cysts settle down in the intestine and become mature. The hydatid cyst is then, in reality, the larval form of the parasite. In cattle and sheep they rarely exceed 7 cm. in diameter and may be single or multiple. In man they grow larger, often about 25 cm. in diameter, and they have been reported to weigh 45 pounds.

Two types of cysts have been recognized. One, which is usually called unilocular, is made up of a cyst wall composed of several layers; it contains muscle-fibers, excretory vessels, and is rich in glycogen. This type may never develop daughter-cysts or scolices. On the other hand, daughter-cysts may bud off from the germinal layer into the cavity of the cyst, and from

these daughter-cysts granddaughter cysts and even great-granddaughter cysts may form. From the walls of each of these cysts countless numbers of scolices may bud, each capable of developing into an adult worm if it finds suitable lodgment. The fluid of the cyst is, of course, primarily obtained from the blood of the host. It is light yellow, neutral or slightly acid in reaction, and its specific gravity is from 1.009 to 1.015. It contains 15 per cent. inorganic salts, some sugar, amino-acids, succinic acid, and cholesterol. Malenjuk says that the fluid is lacking in albumin, mucin, and epithelial cells. As the cyst grows it encroaches on the tissues of the organ and many pathologic changes occur in the tissue surrounding it. It may readily be seen that the cyst fluid of echinococcus resembles only two other biologic fluids. The one is cerebrospinal and the other is the fluid obtained from certain hydronephroses. From a diagnostic standpoint this must be taken into account in determining the presence or absence of hydatids in central nervous tissue and kidneys.

The second type of echinococcus cyst is spoken of as *Echinococcus multilocularis*. This cyst was originally regarded as a colloidal tumor until Zeller and Virchow showed it to be parasitic in origin. The parasite varies in size from a few centimeters to about 18 cm. in diameter. Its cut surface shows a honeycomb structure which is due to the presence of numerous cysts embedded in soft connective-tissue stroma. The cysts are surrounded by a pellucid and laminated cuticle and each contains fluid and globules of fat, bile-pigment, and hematoidin. Scolices are not found in all these cysts. It is the rule for these cysts in man to degenerate. At certain stages large cavities form, filled with purulent viscid fluid. Later on they may ulcerate. Whether these two types of cysts represent different parasites or the same parasite under different environments is not known. Both views are held. If they represent different parasites, the adult form of *E. multilocularis* has never been seen. Smith, who wrote a masterful thesis on the subject of *E. multilocularis*, contends that it is a very common parasite in Australia. He has found cysts 1 mm. in diameter which at that

stage contain multiloculi. The largest cysts are distinctly multiloculated, and these he has seen in sheep, pigs, and in several instances, in Australia, in man. In collecting 1000 multilocular tumors he did not find a single unilocular hydatid. He believes that a thorough search should be made for another adult *Tænia*, yet this is somewhat confusing, since the geographic distribution is apparently not so clean cut as has been believed.

GEOGRAPHIC DISTRIBUTION

The distribution of the disease has been rather thoroughly worked out. With the exception of Smith's report cysts of *Echinococcus multilocularis* have been found only in certain parts of the world included in two regions. One comprises Southern Germany, Switzerland, and the Austrian Alpine region; the other, southwestern Russia and Siberia. *E. unilocularis* is most common in Iceland, Australia, New Zealand, Argentina, and Uruguay. It is fairly common in Italy, Greece, and the steppes of Russia, and quite a few cases have been reported from Germany, certain parts of France, Armenia, and England. Although many cases have been reported from the United States and Canada, very few have occurred in natives of these countries.

It is easily understood why hydatid disease should be common in certain countries and not in others. If the statistics on the subject are observed it is quite evident that the countries in which hydatid disease is most prevalent are the countries in which sheep and cattle are raised extensively, and countries in which public health measures are not well outlined and enforced. For years in the United States it has been against sentimental principles to allow dogs to eat sheep. This in the West is considered almost a crime, and some ranchers in the early days even lost their lives, to say nothing of the dog's, because of owning a dog who ate sheep. The chief mode of dissemination is through the dog who becomes infected from eating the cysts contained in infected sheep or pigs which are not protected from preying dogs. In Iceland the dogs are allowed to eat sheep infected with echinococcus and the owners of the dogs live with them as intimately

as with their own fellow-countrymen, often eating from the same dish and sleeping side by side. In South America the percentage of infection in children is quite high. In Argentina 26.2 in every 100 cases occur in children under four years. As Dévé says, this is the age in which the child, like the dog, walks on all fours, and the intimate association of the two undoubtedly leads to this high percentage of infection. Direct contact, then, between man and dog is responsible for a great percentage of the cases. The second great mode of dissemination of the disease is through the ingestion of fresh vegetables and fruits contaminated by the feces of dogs who, having access to infected sheep and pigs, become infected and harbor the adult form. Already in some of the South American States very definite measures have been instituted to protect persons against eating contaminated vegetables and fruits. Placards are posted to warn the people to wash well and to cook fresh foods.

The percentage of infection in dogs parallels that in man. Thus in Iceland 28 per cent. of the dogs are infected, in Australia from 40 to 50 per cent., and in continental Europe from 4 to 7 per cent. The only authentic record I can find of the presence of the adult type in America is that of Curtise, who found it in one dog in Washington, D. C. The infection in cattle, pigs, and sheep also runs parallel with the infection in man and dogs. Thus in Iceland and India one-half to three-fourths of all the domestic animals are infected. The statistics in Germany vary from 5 to 65 per cent. in different localities. In the United States they vary considerably with communities and with years, usually occurring spasmodically. The disease has been reported from Maryland, District of Columbia, Missouri, Nebraska, Virginia, and Louisiana. In New Orleans, in the examination of 2000 hogs, 117 were found to be infected.

The percentage of infection in man is difficult to estimate; in Iceland it is probably from 2 to 15 per cent.; 3000 cases were reported from Australia between the years 1861 to 1882. The percentage of cases in the German states varies from 0.11 to 2.43. There had been 970 cases in the hospitals of Buenos Aires up to 1901.

The cases recorded in the United States were first collected by Osler in 1882, who collected 61 cases from the United States and Canada. In 1895 and 1896 Sommer collected 100 cases, some being duplicates of Osler's. There remained from the combined reports 110 cases. Lyon in 1902 added 131, making in all 241 cases. The distribution according to the countries from which the patients had emigrated is shown in Table I. In the cases in which the nativity is recorded 91 per cent. of the patients were foreign born and 9 per cent. were natives. One patient was from the United States, 2 from Canada, 10 were negroes; 4 born in the United States. It is impossible to conclude from the data at hand whether any or all of these patients (9 per cent.) had traveled or lived abroad, and at what time their disease appeared in relation to such travel. Since the foregoing reports 68 cases have been reported from North America (Table II). I am reasonably certain that only 4 of these patients were native-born Americans. It is very difficult to collect the cases and to be certain of the nationality of the patients. I do not, therefore, offer this as an absolute number of reported cases.

TABLE I

NATIVITY OF PATIENTS WITH ECHINOCOCCUS DISEASE REPORTED FROM NORTH AMERICA

	Before 1902 (Lyon).	After 1902.
Iceland	58	5
Germany	23	9
Italy	19	19
England	14	3
Ireland	3	4
France	3	0
Russia	4	6
Syria	2	1
Argentina	1	2
Azores	1	0
Austria	1	2
Denmark	1	0
Japan	1	0
Mexico	1	0
Sweden	1	1
United States	5	6
Canada	2	2
Negro (nativity unknown)	6	0
Greece	0	17
Turkey	0	1
Armenia	0	5
Roumania	0	1
Spain	0	1
Albania	0	1
Wales	0	1
Other foreigners	3	0
	149	87

TABLE II

CASES OF ECHINOCOCCUS DISEASE REPORTED IN THE LITERATURE AFTER 1902

Author.	Date.	Sex. Age.	Nativity.	Residence.	Location of cysts.	Year of infection.
Fowler	1901	F.—28	Italy	New York	Liver	1900
Hayes	1902	M.—32	Italy	New York	Right kidney	1901
Stone	1903	M.—40	Armenia	Massachusetts	Liver and lung	1902
Garrett	1906	F.—53	America, Colorado	Maryland	Right liver and right lung	1906
Henry	1906	F.—30	England	Montreal	Liver	1905
Henry	1906	M.—37	Ireland	Montreal	Liver, peritoneum	1905
Henry	1906	.....	.....	Montreal	Liver	1867
Henry	1906	.....	.....	Montreal	Uterus	1871
Henry	1906	M.—69	.....	Montreal	Liver	1896
Henry	1906	M.—	.....	Montreal	Liver	1895
Henry	1906	F.—36	Iceland	Montreal	Liver	1900
Henry	1906	F.—30	England	Montreal	Liver	1905
Henry	1906	M.—37	.....	Montreal	Omentum, peritoneum	1905
Cheney	1906	M.—7	Italy	California	Liver	1897
Cheney	1906	M.—10	Argentina	California	Liver	1905
Hartley	1906	M.—25	Italy	New York	Liver	1897
Hartley	1906	M.—32	Austria	New York	Liver	1896
Hartley	1906	M.—28	Germany	New York	Liver	1900
Hartley	1906	M.—34	Italy	New York	Pelvis, peritoneum	1898

TABLE II (continued)

Author.	Date.	Sex. Age.	Nativity.	Residence.	Location of cysts.	Year of infection.
Ashton	1907	M.—30	.....	Missouri	Peritoneum	1906
Downes	1915	M.—49	.....	New York	Kidney, left	1915
Fay	1915	M.—41	Germany	Iowa	Liver	1914
Fowler	1916	F.—21	.....	New York	Liver, left	1915
Kerwin	1916	F.—44	America	Missouri	Pelvic peritoneum	1914
Hawkes	1916	.....	Armenia	Rhode Island	Neck	1901
Hawkes	1916	M.—	Armenia	Rhode Island	Liver	1907
Hawkes	1916	F.—	Italy	Rhode Island	Liver	1909
Hawkes	1916	M.—	Turkey	Rhode Island	Liver	1915
Phemister	1917	F.—38	Greece	Illinois	Liver	1916
Walker and Cummins	1917	M.—31	Greece	California	Tibia	1915
Russell and Kilbane	1917	M.—46	Italy	New York	Kidney, right	1916
Johnston and Willis	1917	F.—48	America	Virginia	Liver	1915
Johnston and Willis	1917	F.—62	America	Virginia	Liver	1914
Cahana	1917	M.—45	Greece	Wisconsin	Liver	1917
Cahana	1917	M.—29	Greece	Wisconsin	Spleen	1917
Davis and Balboni	1917	M.—34	England	Massachusetts	Liver	1875
Davis and Balboni	1917	M.—26	Armenia	Massachusetts	Liver	1898
Davis and Balboni	1917	F.—31	Ireland	Massachusetts	Liver	1898
Davis and Balboni	1917	M.—19	Russia	Massachusetts	Liver	1899
Davis and Balboni	1917	M.—27	Greece	Massachusetts	Liver and omentum	1899
Davis and Balboni	1917	M.—52	Ireland	Massachusetts	Liver and peritoneum	1904
Davis and Balboni	1917	F.—24	Italy	Massachusetts	Liver	1905
Davis and Balboni	1917	M.—49	Sweden	Massachusetts	Liver	1906
Davis and Balboni	1917	M.—22	Russia	Massachusetts	Pleura and peritoneum	1906
Davis and Balboni	1917	M.—26	Italy	Massachusetts	Bile-duct and peritoneum	1907
Davis and Balboni	1917	M.—23	Greece	Massachusetts	Omentum	1907
Davis and Balboni	1917	M.—35	Greece	Massachusetts	Liver	1907
Davis and Balboni	1917	M.—33	Iceland	Massachusetts	Liver	1908
Davis and Balboni	1917	M.—20	Italy	Massachusetts	Liver	1908
Davis and Balboni	1917	M.—32	Greece	Massachusetts	Liver	1909
Davis and Balboni	1917	F.—48	Germany	Massachusetts	Retroperitoneal	1909
Davis and Balboni	1917	M.—23	Italy	Massachusetts	Kidney, left	1914
Davis and Balboni	1917	F.—35	Greece	Massachusetts	Kidney, left	1914[1]
Davis and Balboni	1917	M.—34	Italy	Massachusetts	Liver and right kidney	1914[1]
Davis and Balboni	1917	M.—44	Italy	Massachusetts	Retroperitoneal	1915[1]
Davis and Balboni	1917	M.—34	Syria	Massachusetts	Liver	1915[1]
Davis and Balboni	1917	F.—44	Italy	Massachusetts	Liver	1915
Davis and Balboni	1917	M.—22	Greece	Massachusetts	Liver and peritoneum	1914
Davis and Balboni	1917	M.—24	Italy	Massachusetts	Brain	1913[1]
Davis and Balboni	1917	M.—49	Italy	Massachusetts	Liver	1914
Davis and Balboni	1917	M.—27	Italy	Massachusetts	Liver, omentum, lung	1912[1]
Davis and Balboni	1917	M.—28	Albania	Massachusetts	Liver	1916
Crow	1918	M.—30	Spain	Washington	Lung, right	1917
Jones	1920	M.—24	Italy	New York	Liver, spleen	1920
DaCasta	1921	M.—28	Greece	Pennsylvania	Liver	1920
McKenzie	1903	M.—41	Roumania	Montreal	Liver	1902
Helms	1914	M.—45	Greece	Florida	Peritoneum (liver)	1913
Helms	1921	F.—35	Italy	Florida	Liver	1902[2]

[1] Positive complement fixation.
[2] Personal communication.

TABLE III

CASES OF ECHINOCOCCUS DISEASE FROM THE MAYO CLINIC

Case.	Sex. Age.	Nativity.	Residence.	Location of cysts.	Year of infection.
J. L.	F.—45	Germany	Minnesota	Liver	1898
S1,238	M.—33	Germany	Minnesota	Left lobe of liver	1904
35,423	M.—33	Germany	Minnesota	Liver	1904
G4,871½	M.—37	Wales	Pennsylvania	Liver	1905
M2,968	F.—47	Germany	Minnesota	Liver	1906
9,985	M.—30	Russia	Canada	Gall-bladder	1908
14,551	M.—37	Iceland	North Dakota	Left lobe of liver	1908
18,143	M.—35	Iceland	Minnesota	Right lobe of liver	1908
22,233	M.—48	Germany	Iowa	Left lobe of liver	1909
52,134	F.—41	Argentina	Nebraska	Liver	1911
85,620	F.—27	Iceland	Canada	Liver	1913
130,474	F.—38	United States	Minnesota	Liver	1915
135,830	M.—54	Russia	South Dakota	Liver	1915
149,714	M.—45	Germany	Iowa	Abdominal wall and liver	1916
151,659	F.—38	Greece	Minnesota	Left lobe of liver	1916[1]
145,012	M.—	United States[2]	Nebraska	Lung	1916
210,825	F.—24	Iceland	Minnesota	Liver	1917
195,506	M.—34	Greece	Illinois	Liver	1917[1]
185,909	M.—26	Greece	South Dakota	Liver	1917
248,755	M.—48	England	Canada	Right lobe of liver	1918
258,261	M.—67	Canada	Minnesota	Liver	1919
271,000	M.—64	Austria	Colorado	Liver	1919
323,329	M.—30	Greece	Ohio	Liver	1920[1]
309,608	M.—34	Greece	Oklahoma	Liver	1920[1]
323,299	F.—44	Russia	North Dakota	Spinal cord (ex liver)	1920[1]

[1] Positive complement fixation.
[2] Traveled in Philippine Islands in 1908.

TABLE IV

ORGANS AFFECTED IN CASES OF ECHINOCOCCUS DISEASE REPORTED AFTER 1902

Organs.	Cases.
Liver	69
Peritoneum	10
Lungs	4
Kidneys	4
Omentum	4
Spleen	2
Retroperitoneal	2
Spinal cord	1
Brain	1
Abdominal wall	1
Gall-bladder	1
Common bile-duct	1
Uterus	1
Neck	1
Tibia	1
Pleura	1
	104

Twenty-five patients with echinococcus disease have been observed in the Mayo Clinic in the history of the institution (Table III). Of these, 2 are natives of the United States. The organs infected are shown in Table IV. It is interesting to speculate on when these patients became infected. Many of those reported to be foreign born were found to have the infection after they had lived in America for many years. In the case which DaCosta reported the patient had lived in America nine years; DaCosta does not believe that the condition in this case was contracted outside the United States. Such a statement is hazardous. Leuckart showed that the disease is one which progresses very slowly; in pigs the organism may develop from 15 to 20 mm. in five months; growth after this is extremely slow. Cases have been reported in which the infection has been known to exist from thirty to forty years, and it is really quite impossible to determine the duration of any given infection. It is quite possible that some of the cases in the foreign born were actually contracted in the United States, and that some, at least, of the cases reported in the United States in natives undoubtedly were contracted in this country. The fact that the hogs and cows in this country are infected probably means that dogs harbor the parasite, and were it not for the mode of living and the sentimental and practical hatred for the "sheep-eating" dog, it would not be long before the United States would have its share of this disease.

An erroneous idea of the geographic distribution of echinococcus disease may be obtained from the study of the statistics from North America. Unless they are interpreted in the light of immigration statistics they are of little value. Of the 241 cases which Lyon collected, the nationality of the patients was stated in only 149. In my collection of cases from 1902 to the present time the nationality is stated in 87. Lyon reported 58 cases from Iceland out of 149. In my series only 5 out of 87 cases are reported from Iceland; if the ratio had remained the same there should have been 27 cases. A study of the statistics of immigration shows that from 1902 on there has been scarcely no immigration from Iceland to North America. No cases were

reported in Greeks prior to 1902, but since then 17 cases have been reported. In 1903 the number of immigrants from Greece had risen from two to four times the number of those who came from Greece yearly preceding 1902. Had the ratio remained the same in the case of Italians there would be 8 cases since 1902 instead of 19, and from Italy also immigration has doubled or tripled since about 1900. From Germany 12 cases would have been reported instead of 9 had the ratio remained the same as prior to 1902. However, the immigration from Germany has constantly been falling off. Only 3 cases have been reported from South America and 1 from Australia, although these countries are perhaps most severely infected. This small number is explained by the fact that there is scarcely any immigration from these countries to the United States. Thus, in computing the possibility of a given foreign patient having echinococcus it is quite necessary to have some idea of the ratio of the disease found in North America in that particular race and not the absolute numbers that have been reported. A given Icelander at the present time has about the same chance of being infected when he comes to North America as he had prior to 1902, and yet very few Icelanders have been reported with the disease since that time. The influx to North America from Iceland began in the year 1874 when the first group of Icelanders came to Manitoba. The first mention of cases reported in Icelanders in North America was from Manitoba, or from Icelanders who had gone from Manitoba to other parts of the country.

FACTORS INFLUENCING THE SPREAD OF THE DISEASE

The factors necessary for the prevalence and spread of the disease are summed up by Stirling and Verco. They are as follows:

1. A sufficiency of dogs infected with *Tænia echinococcus*, by which means the supply of ova is kept up.

2. Many animals, such as the domestic herbivora, particularly sheep, capable of serving as the intermediate host of the bladder-worm.

3. Conditions favorable to the entrance of the tenian ova

into the alimentary canal, either of man or of the ordinary intermediate hosts.

4. Facility of access of dogs to the carcasses, or hydatid-containing organs, of the intermediate hosts, such as the domestic herbivora, by which means the supply of *Tænia echinococcus* is kept up.

The steps necessary to the elimination of the disease are easily deduced; fortunately they have been automatically taken care of in the United States. The dogs infected are limited because dogs usually are not allowed access to contaminated herbivora. Man does not have access to the eggs or larval echinococci because the dogs are not generally infected, nor do they come in contact with man in such a manner that infection could take place.

ORGANS INFECTED

The liver is the organ most often infected. Various statistics are given, but those of Vegas and Cranwell in their review of 2027 cases are of particular interest. According to them the liver is the seat of infection in 74.9 per cent., the lungs in 8.5 per cent., the muscles in 5.7 per cent., the spleen in 2.3 per cent., the kidneys in 2.1 per cent., the brain in 1.4 per cent., the bone in 0.9 per cent., and the various other organs in 4.2 per cent. Alexinsky, reviewing 950 cases, found that 1.9 per cent. involved the bone. Gangolphe reports 1.7 per cent. bone infections in 3000 cases. The statistics of Ward are as follows: Of 1806 cases, 1011 were found in the liver, 147 in the lung, 126 in the kidney, 42 in the spleen, 53 in the circulatory apparatus, 91 in the cranial cavity, 62 in the peritoneum, 75 in the pelvis, and 60 in the female genital organs. In the cases which Dévé studied and reported in children 76 per cent. showed liver involvement.

Table IV lists the organs infected in the cases discussed in this paper. The liver was involved in 76.3 per cent. of these cases.

DIAGNOSIS

It is highly important that echinococcus disease should be diagnosed before surgical or other treatment is instigated.

The reasons are clearly defined. As early as 1887 Volkman pointed out the danger of puncture, and Lebedeff and Andreen and Alexinsky showed that following the puncture of a hydatid cyst implantation cysts might occur anywhere the fluid with daughter-cysts happened to come in contact with other organs. Not only is there danger of metastasis but also there is very serious danger of an anaphylactic shock following the spilling of fluid into a cavity like the peritoneum. Certainly the condition presents very definite means of diagnosis. The only definite clinical sign of hydatid disease is that of Santoni; other signs and symptoms are referable to the organ and not to the disease. The examination of the blood for its cellular constituency offers but little information. Perhaps 60 per cent. of patients with hydatid disease show some eosinophilia, varying from 2 to 60 per cent., but the vast majority have an eosinophilia no higher than 6 per cent. The *x*-ray offers some help. The lesions appear as dark shadows and, if they appear in the liver, the diaphragm is usually shown elevated in a dome shape, with the convexity pointing toward the base of the lung, which may distinguish it from fluid in the chest. A roentgenogram of bone infected with echinococcus has been described by Harris. This showed a slight area of bone absorption not unlike an osteomyelitis. In the lung the cyst resembles an abscess and is usually quite well defined.

The absolute diagnosis is often made at the operation or necropsy, and consists in finding hooklets or daughter-cysts, or characteristic fluid whose properties are well known, or in identifying the histology of the cyst wall. Diagnosis of hydatid disease may be made, however, with very great certainty by some of the biologic tests which have been proposed. Usually one test will suffice; however, the application of more than one is, of course, desirable. If there is any suspicion that the patient under examination is suffering from hydatid disease he should be given the benefit of the doubt, and no exploratory puncture made. If it is necessary or desirable to explore, it should be done following a wide incision and thorough walling off surrounding structures, and the surgeon should be prepared to

remove the cyst *in toto* or to treat by marsupialization or proper drainage. The tests which follow have been devised for diagnosis.

THE MIOSTAGMIN REACTION

This test, the principle of which was devised by Ascoli in 1910, has been used for the diagnosis of echinococcus disease by Izar and Brugnatelli. It consists of counting the number of drops which flow from the Traube stalagmometer in a unit of time: 9 c.c. of serum or diluted blood is mixed with 1 c.c. of antigen, the antigen being prepared from cyst fluid or cyst membrane. This antigen is an alcoholic extract which may be used either as such or evaporated and taken up in distilled water. The number of drops flowing from the stalagmometer is counted at once, and again after an incubation of two hours at 37° C. Decrease in surface tension or an increase in the number of drops flowing from the stalagmometer indicates a positive reaction. The increase is usually about 2.5 to 4 drops. Izar tested 3 pigs and 4 cows suffering from the disease, all of which showed positive reaction. Controls were run on 2 pigs and 3 cows, with negative results. Brugnatelli tested 9 cases of echinococcus in man, using a water solution of cyst fluid as antigen. All 9 gave positive miostagmin reactions, but only 8 of these were positive with complement fixation; 3 negative cases were used as controls.

COMPLEMENT-FIXATION TEST

It has been shown that hydatid disease produces in the host antibodies of the third order (Ehrlich). Because of this fact it is possible to diagnose the disease by complement fixation, as in the case of syphilis. The first man to make use of this fact was probably Ghedini, who in 1906 proposed the application of the Bordet-Gengou reaction in the diagnosis of hydatid disease. Weinberg and Parvu about the same time investigated this reaction and, while their results are not altogether satisfactory, they nevertheless obtained rather definite results with regard to complement fixation in hydatid disease. Following these workers many others have applied, with a very high degree of

success, the complement-fixation reaction to hydatid disease. Weinberg, who has published the most important statistics on the subject, examined 52 serums obtained from cases which clinically could be diagnosed as possible hydatid disease; 27 of these cases proved to be hydatid, and in these he obtained 26 positive reactions. The serum which gave a negative result became positive twenty days following operation. Laubrey and Parvu obtained two positive results in 3 cases. Rosello examined 12 cases of hydatid disease, 10 of which gave positive reaction; the 2 others were doubtful. Lorentz published reports of 9 cases, all of which were positive. Eckenstein reported the result of this test in 18 possible cases of hydatid disease, 9 of which were verified at operation. Of these 9 cases, 8 gave positive reactions and 1 gave a false positive, but on being repeated three times was negative. This is the only false positive I have been able to find reported in the literature. Luridiana tried the test in 10 cases, obtaining 8 positives. In the Mayo Clinic complement fixation has been found positive in the only 5 cases tested. No false positives have been obtained in 10 control cases. It is possible that a degenerating suppurating hydatid cyst or a cyst which is calcified does not produce enough antibodies to give a positive reaction, and this probably explains the few negative results that have been obtained. On the other hand, the reaction is positive in cases in which operation has been performed many months before. Weinberg says that it is positive from two weeks to six years after operation.

The reaction has never been obtained from spinal fluid of patients suffering from hydatid cyst. The technic of the test is, like the Wassermann test, more or less individual. Various methods of preserving the antigen or cyst fluid have been proposed, and each seems equally satisfactory in the hands of the individual technician. In the Mayo Clinic sterile fluid is obtained at the time of the operation, or fluid is obtained from a sheep or pig hydatid cyst and preserved with a little phenol. The blood of the patient after clotting is centrifuged and the serum is used as in the Wassermann test. The usual method is to set up three tubes with three controls. The first tube receives

5 drops of antigen, the second tube 2 drops, and the third tube 1 drop. Into the first tube is then placed 1 drop of the patient's serum, the second tube receives 2 drops, and the third tube 5 drops. Complement is added to each tube and the tubes with their controls are incubated for one hour, at the end of which time cells are added with amboceptor and the results read, as in the case of a Wassermann reaction. For the hemolytic system we have used human red blood-cells with antihuman dog amboceptor. The complement is obtained from guinea-pigs. As a control for this reaction a known Wassermann negative blood and a positive Wassermann blood are set up. In all of the tests we have not noted a false positive, despite the fact that our antigen contained large amounts of cholesterol.

In general, it would seem that this fixation test is to be treated much as the Wassermann or any other complement fixation, except in echinococcus disease it does not give false positives, so that a positive result is almost sure evidence of echinococcus infestation. One negative result is, of course, difficult of interpretation, although it will mean in the vast majority of cases that the patient does not have echinococcus disease, or, if hydatids are present, it indicates a suppurating process or a calcified cyst.

THE PRECIPITIN REACTION TEST

This test was devised by Fleig and Lisbonne in 1907 and has proved of value in the hands of several diagnosticians. Welsh and Chapman the following year modified the test to some extent, and in their hands it has been a very important means of diagnosing echinococcus disease. The technic is much the same as that used for any precipitin reaction, and depends on the presence of specific precipitins in the serum of the patient, which, when brought in contact with antigen, that is, hydatid fluid, produces a white flocculation. The technic of the test is as follows:

Hydatid fluid is obtained aseptically from a cyst of sheep or of man, is filtered through a Chamberland filter, and sealed in sterile ampules for use. One cubic centimeter of this fluid is used in the test, and to it is added from 8 to 20 drops of the

patient's serum. The tube containing the mixture is put aside at room temperature for from eighteen to twenty hours, at the end of which time if the reaction is positive a more or less dense white precipitin is present in the bottom of the tube. Controls are set up at the same time and these should remain clear. I can find reported in the literature only 37 proved cases of echinococcus disease tested in this manner. Of these, 29 (78.4 per cent.) were positive, 2 gave negative results, and 6 were doubtful. In the hands of Welch and Chapman 19 positive reactions were obtained in 20 cases. No false positives are recorded in literature. This test reminds one very much of the Sachs-Georgi test for syphilis, and perhaps gives a little higher percentage of positives without giving false ones.

ABDERHALDEN REACTION

The Abderhalden reaction has been applied for the diagnosis of hydatid disease by Giani. He prepares the antigen from the cyst membrane and the hydatid fluid which, after being properly extracted, is preserved in chloroform or toluol. Equal parts of this antigen and fresh serum from the patient are emulsified and dialyzed against 20 c.c. of distilled water for eighteen hours at 37° C.; 10 c.c. of the dialyzate is mixed with 0.2 c.c. of 1 per cent. ninhydrazene and boiled for one minute. The usual reaction is noted if the patient suffers from hydatid disease; 14 patients were tested in this manner, 7 of whom had echinococcus. All 7 gave positive Abderhalden reactions and the remaining 7 were negative.

INTRADERMIC REACTION

As in many other conditions, it is possible to demonstrate anaphylaxis or allergy in the skin of patients suffering with echinococcus disease. Puntoni tested 3 cases of echinococcus disease, using a type of cutaneous test suggested by the work of von Pirquet. He also tested 1 case, using the cyst fluid in the eye, hoping to obtain an ophthalmic reaction. His results were negative. Bordin and Laroche attempted to diagnose the con-

dition by using the fluid intradermally, and concluded that this test is not specific. Casoni studied skin reaction in hydatid disease, publishing his results in 1912 to 1914. He first attempted to apply the cutaneous test of von Pirquet, cleansing the arm with ether, making three abrasions, on the first of which he placed a drop of hydatid fluid, and on the second an extracted membrane with hydatid fluid; and the third was used for control. The test was not definite enough from which to draw conclusions. He then devised an intradermic test which is apparently quite satisfactory. He obtained cyst fluid from a cow, and filtered it four or five times. Into every 20 c.c. he put 1 drop of pure phenol and preserved it in the ice-box; 0.5 c.c. of this fluid was injected into the skin as in the test of Manteaux, and this was controlled with an equal amount of physiologic salt solution. If the test was positive within from three to twelve hours a large wheal formed at the sight of inoculation. This varied from a diameter of 3 to 5 cm. The wheal was erythematous with an edematous infiltration, accompanied by a local rise in temperature and itching. There was no general response, such as a rise in body temperature, or general pruritus, or urticaria. Extracts of the membrane when used in this manner responded but weakly and in only a certain percentage of cases. Casoni used the test on 25 patients, 7 of which were proved to have hydatid disease. He obtained 8 positive results; 1 was a false positive. Luridiana has used this test with very good results. He preserved the hydatid fluid with chloroform. In his first report he tested 6 patients, who proved at operation to have hydatid disease; 5 of these gave positive reactions and 1 gave a negative, followed by a positive reaction. Twenty controls were all negative. In his second report he compared the findings in 10 cases of hydatid disease. The intradermic reaction was positive in 7, complement fixation in 8, precipitin reaction in 5. Gasbarrini obtained 11 positive reactions in 12 patients afterward proved to have hydatid disease. The twelfth had a suppurating cyst. He obtained no false positives in a number of negative cases.

CUTANEOUS TEST

Without the knowledge of the results which had previously been obtained by cutaneous tests in cases of hydatid disease I thought it might be possible to obtain a specific allergic phenomenon in these cases. Hydatid fluid was obtained from a cyst of a patient and from a cyst of a sheep, which was preserved with phenol. The test was performed as in the case of other skin sensitization reactions. The skin of the forearm was cleansed with alcohol and dried. Three abrasions were made in the usual

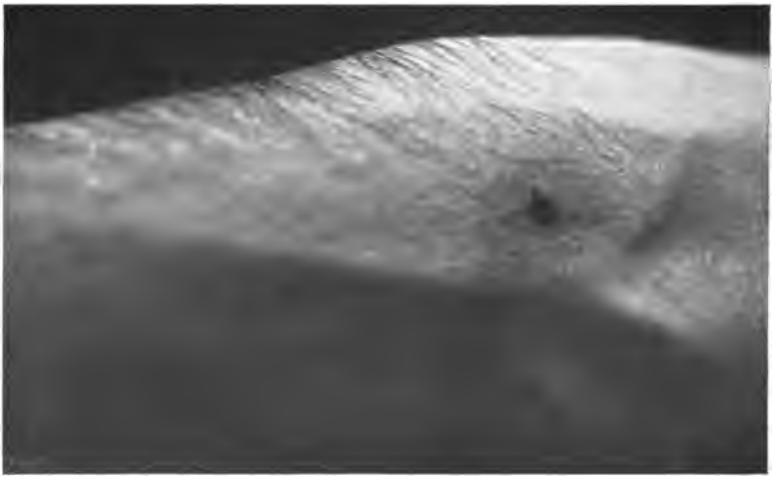

Fig. 141.—Cutaneous test for echinococcus disease.

fashion. Hydatid fluid was placed on two, the third remaining as a control. Three patients who later at operation proved to have hydatid disease were tested in this fashion, and all gave positive results. The reaction consisted in a raised wheal, white in its center zone, quite red in the interior zone, and erythematic on the outer zone (Fig. 141). There was no itching; the reaction appeared within twenty minutes, and subsided at the end of about three hours.

Twenty patients in which there was no suspicion of hydatid disease were tested, all of whom proved negative.

SUMMARY

It seems quite evident from the study of laboratory methods that echinococcus disease can be diagnosed fairly accurately in the vast majority of cases without either an exploratory puncture or an exploratory incision. In view of the serious consequences following exploratory puncture of a hydatid cyst some biologic test should be performed before resorting to this procedure in any tumor which is suspected of being an echinococcus cyst. Echinococcus cyst need be suspected rarely in a native North American, and in dealing with foreigners the percentage of infection in the various countries should be taken into consideration and not the number of cases reported in natives of that country in North America. If it is necessary to explore, this should be done through a wide incision with ample protection by walling off and scrupulous surgical technic.

From the purely abstract scientific standpoint it is quite evident that hydatid infection causes a very definite biologic reaction in the host. Certain antibodies of a very specific nature are formed through the growth of this organism. There is perhaps no other disease that gives so clean-cut a reaction in so many different tests as does echinococcus, and for this reason it is not unlikely that a study of the antibodies formed in this condition offers more certain results from the standpoint of the factors of immunity involved in the production of antibodies than any other disease that could be studied.

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RESULTS OF EXPERIMENTAL STUDIES ON FOCAL INFECTION AND ELECTIVE LOCALIZATION[1]

EDWARD C. ROSENOW

MANY facts indicate that localized infections, often insignificant and symptomless in themselves, may be the source of systemic disease. Focal infections are present in demonstrable form in a high percentage of the sick, both young and old. Thorough removal of foci of infection is followed by improvement in general health and frequently by improvement or cure of distant local and systemic diseases, provided such diseases are not too far advanced. Indeed, improvement has occurred so often that many physicians have come to regard these observations as proof of etiologic relationship; and if improvement does not follow removal of a given focus, it is considered presumptive evidence either that the particular operation was not properly performed or that other foci exist. Exacerbation of systemic conditions immediately following the removal of certain foci of infection further suggests causal relationship. The idea of an etiologic relationship is not new, and relief of systemic conditions following the removal of foci of infection is mentioned in the older medical literature. But it was not until after Billings[2, 3] and his co-workers[10, 37] reported their clinical observations and correlated experimental studies in animals that the importance of this interrelationship became more generally recognized.

The original studies included the consideration of localized infections in various parts of the body, but especially those in tonsils, sinuses, and teeth. Numerous papers on various phases of the problem soon appeared. The combined clinical and experimental studies of Gilmer, Hartzell, Hartzell and Henrici,

[1] Presented before the Section on Stomatology at the Seventy-second Annual Meeting of the American Medical Association, Boston, June, 1921.

Gilmer and Moody, and Moody emphasized the importance of dental foci. The contributions, considering the subject from the clinical standpoint, by C. H. Mayo, Fischer, Black, Ulrich, Post, White, Irons, Brown and Nadler, Daland, Barker, Duke, and others did much to awaken interest among members of the medical and dental professions in this important cause of disease.

Experimental studies have shown that foci of infection in a given case may harbor the same types of bacteria that are found in distant lesions; that intravenous injection of the freshly isolated strains into animals, both from the focus and from the diseased organs, is followed by localization and lesions in organs corresponding to those involved in the patient from whom the bacteria were isolated; and that, from the lesions produced experimentally, the organism may be isolated in pure culture, the disease again reproduced, and the organism again isolated. The usual requirements for the demonstration of causal relationship between extraneous parasites and disease were fulfilled.

Many puzzling questions arose. Granting that causal relationship existed between localized infections in tonsils and teeth and a distant lesion, why should some persons develop ulcer of the stomach, others lesions in the joints, and still others lesions of the gall-bladder, and so forth?

During my investigations on the transmutation of pneumococci and streptococci I found that variation in oxygen tension and growth in symbiosis with other bacteria, conditions usually present in foci of infection, tended to produce marked changes in this group of micro-organisms, and that when strains of low virulency were rendered more virulent by successive animal passage localization shifted from areas of relatively low available oxygen supply, such as heart valves and periarticular structures, to those of higher oxygen supply, such as muscles, myocardium, stomach, gall-bladder, kidneys, and lungs. By the use of special methods[28] in which a gradient of oxygen tension was afforded the bacteria and in which fresh cultures were injected intravenously into animals, it became apparent that the specific infecting powers of the bacteria in the focus were the chief factor that determined the place of localization in remote structures.

In a paper[29] which I presented before this Association six years ago it was shown that streptococci isolated from foci and systemic lesions tended to localize electively in the respective tissues in appendicitis, ulcer of the stomach, cholecystitis, rheumatic fever, erythema nodosum, herpes zoster, myositis, chronic septic endocarditis, and epidemic parotitis. Since then I have reported similar results in diseases of the nervous system, such as infective transverse myelitis, multiple neuritis, neuralgia, and epidemic poliomyelitis, in diseases of the eye, and nephritis. Detailed considerations of these studies may be found in my original papers published in the *Journal of Infectious Diseases* and the *Journal of the American Medical Association.* The results in ulcer have been verified and extended by Helmholz and Hardt, and those in cholecystitis by Brown. The elective localizing power of streptococci and colon bacilli from urinary infections has been demonstrated by Helmholz and Beeler. Bumpus and Meisser have recently shown that pyelonephritis may result from the elective localization of streptococci from foci of infection around the teeth and in tonsils, and that infections of the bladder may occur in the same manner.

Inability to obtain evidence of the elective localizing power of bacteria in the hands of some observers, as pointed out by Gay, may well be explained by insufficient attention to technical details. Henrici, for example, first plated his material aërobically on blood-agar and made inoculations in animals with subcultures of strains of streptococci fished from single colonies on an average of one week after isolation. In Moody's experiments the dose was very much smaller and the animals were allowed to live for a longer time than in my experiments. With regard to the general disease-producing power of streptococci contained in dental and other foci, however, their experimental results were similar to mine. Thus, Henrici produced lesions in joints, muscles, kidneys, myocardium, and arteries with streptococci from dental foci. Moody had similar results. Bull, who failed to corroborate the results in poliomyelitis in his experiments with streptococci, worked under conditions and with a technic which differed from mine in important respects. He studied

streptococci from tonsils in poliomyelitis and from tonsils and teeth of persons who were not suffering from poliomyelitis nor in immediate contact with the disease, but who resided in the midst of a wide-spread epidemic. He injected massive doses of streptococci, grown aërobically at 37° C., chiefly on ascites-glucose-agar slants. I injected various sized doses of streptococci from tonsils, brain, and cord, grown at from 33° to 35° C., in tall columns of ascites-glucose broth, affording a gradient of oxygen pressure. Cognizant of the fact that in poliomyelitis I was dealing with a disease which attacks chiefly infants, young animals were used. The average weight of the guinea-pigs showing positive results in my experiments was 200 gm., that of the rabbits, 600 gm. Only adult guinea-pigs, weighing from 450 to 500 gm., and rabbits averaging 1580 gm. in weight were used in Bull's experiments.

In my own experiments in this field the primary consideration was to determine whether or not foci of infection harbor bacteria, quite without regard to species, which may produce disease in animals corresponding to that found in the patient. The young primary cultures, even if mixed, were often injected. Intensive effort was made to work with the bacteria from the depth of a focus and not merely with those on the surface, which might be a saprophytic flora. Pus was expressed from tonsils. In some instances tonsils were extirpated. The pus in pyorrhea was aspirated from the depths of the pockets by means of a glass pipet. Teeth which showed apical infection or which were non-vital and did not show rarefaction at the apices were extracted for experimental study. The cases were carefully selected.

Very early in the work it was found that the bacteria concerned were often extremely sensitive to oxygen. This was especially true of the streptococci isolated from the joint fluid of patients having rheumatic fever. No growth occurred under either aërobic or strictly anaërobic conditions, but only under conditions of partial oxygen tension. It has frequently happened that aërobic cultures on blood-agar plates from the joint fluid in experimental arthritis and the involved tissues in other

diseases remain sterile when those in tall tubes of glucose-brain broth yield pure cultures of the causative streptococcus. Similarly, aërobic cultures from foci of infection, such as infected dental pulps and granulomas at the root apices of teeth, were often negative when the cultures affording a gradient of oxygen tension yielded the organism which reproduced the disease from which the patient was suffering. For example, in a case of acute iritis the aërobic cultures from the pulp of a non-vital tooth remained negative, while in tall columns of broth a partial tension streptococcus was obtained with which iritis was produced in a series of rabbits, and from the inflamed irises the organism was isolated.[30] Moreover, aërobic cultivation tends to destroy promptly the property on which elective localization depends, whereas partial tension cultures tend to preserve it for a longer time, especially if subcultures are made as soon as abundant growth has occurred. Preserving cultures under suitable conditions in latent life also tends to preserve this property. Thus, a streptococcus from cholecystitis, having marked affinity for the gall-bladder in animals, lost the power to produce lesions in the gall-bladder after four daily subcultures on blood-agar, while in dense suspension in salt solution containing sterile tissue and kept in the ice-chest, the property was preserved for as long as two years. It thus appears that the specific strain may be lost even in the primary culture, unless the culture-medium is particularly favorable for growth, both with regard to available nutritive material and with regard to oxygen tension. The importance of oxygen tension for the cultivation of various streptococci, and the variations in this requirement for growth, have been emphasized especially by Gräf and Wittneben and by Wherry and Oliver.

In my earlier work rather large doses of streptococci grown in tall columns of ascites-glucose broth, with or without sterile tissue, were usually given. However, exceedingly small doses sufficed to call forth specific lesions in some instances. Thus, in herpes zoster the few streptococci contained in a filtrate of ascites-glucose-broth culture localized and produced lesions in the posterior root ganglia and herpes of the skin in the correspond-

ing segment. The objection which has been raised regarding dosage has been met by injecting smaller doses of cultures, and by directly injecting salt solution suspensions of the relatively small number of bacteria from tonsils. Indeed, some of the most specific localizations occurred in the latter experiments. Thus, in myositis, of a total of 35 rabbits injected, 33 (94 per cent.) developed lesions in muscles. This was in sharp contrast to the results obtained following injection of the tonsil pus from 12 persons who were well at the time or who had some ailment not attributable to infection. Of the 24 rabbits injected, only 3 (12.5 per cent.) developed lesions in muscles. Similar results have been obtained in a number of cases of ulcer of the stomach, cholecystitis, nephritis, and neuritis.

In most of the work which I am now reporting smaller doses of streptococci grown in tall columns of glucose-brain broth were inoculated, usually from 0.5 to 5 c.c. for medium-sized rabbits. The glucose-brain broth is prepared by adding to plain peptone broth 0.2 per cent. glucose. The reaction is adjusted to plus 1 and to a hydrogen ion value of 6.7 to 7.2, and the medium is placed in columns from 10 to 12 cm. tall, in 20 by 1.5 cm. tubes, to which approximately 2 gm. of brain substance and several pieces of marble are added before autoclaving. It was found that pieces of brain decolorize methylene-blue, render the bottom of the tube sufficiently anaërobic to grow tetanus spores, and lower the surface tension to a considerable degree. This mediúm has given excellent results. Growth of streptococci is especially rapid. Injections were made as soon as good growth was obtained, in from twelve to twenty-four hours. The animals usually appeared free from symptoms and were chloroformed for thorough examination in from twenty-four to seventy-two hours after inoculation.

RESULTS

In the table are summarized the results obtained from a study of the elective localizing power of streptococci from a series of cases of appendicitis, ulcer of the stomach, cholecystitis, myositis, acute poliomyelitis, neuritis, and sciatica, and, for

comparison, the results obtained following injection of streptococci from miscellaneous sources. The figures indicating the incidence of lesions are given on a percentage basis and hence are directly comparable. In appendicitis, ulcer of the stomach, cholecystitis, myositis, and poliomyelitis the experiments were performed with strains from foci of infection and from the organs involved, whereas in the neuritis and sciatica groups, and in the miscellaneous group, the injections were all made with strains from foci of infection.

FURTHER RESULTS ON ELECTIVE LOCALIZATION OF STREPTOCOCCI

Source of streptococci.	Strains.	Animals.	Percentage of animals showing lesions in												
			Muscles.	Joints and ligaments.	Nerves.	Stomach and duodenum.	Gall-bladder.	Appendix.	Kidneys.	Lungs.	Skin.	Pericardium.	Myocardium.	Endocardium.	Central nervous system.
Appendicitis...	17	71	12	29	0	11	1	**70**	0	0	0	0	9	21	?
Ulcer of the stomach.....	37	168	4	12	0	**68**	21	1	3	0	0	2	3	10	?
Cholecystitis...	12	41	7	17	0	29	**80**	0	5	5	2	0	2	10	?
Myositis.....	28	202	**80**	33	9	13	3	1	9	7	4	4	17	8	?
Acute poliomyelitis.....	22	123	16	15	4	13	2	2	2	11	0	5	7	7	**46**
Neuritis and sciatica.....	10	59	42	15	**66**	5	2	3	12	15	0	5	10	3	14
Miscellaneous..	71	212	12	9	4	9	1	1	9	7	4	0	4	12	?

It will be noted in the table that the highest incidence of lesions in the animals occurred in the organ which was chiefly affected in each of the diseases studied, that the next highest incidence of localization occurred in structures which are not infrequently involved as associated conditions in the respective diseases, and that in the miscellaneous group no high incidence

of localization occurred. Thus, the highest incidence of lesions other than in the stomach was in the gall-bladder, 21 per cent., following injection of the ulcer strains, and in the stomach and duodenum, 29 per cent., following injection of the cholecystitis strains. In myositis the relatively high incidence of lesions in joints and ligaments, 33 per cent., and in the myocardium, 17 per cent., is in accord with what is usually found clinically in this disease. The same may be said of the high incidence of lesions in muscles, 42 per cent., following injection of streptococci from patients whose chief complaint was diagnosed sciatica. Lesions in the pulps of teeth or periapical structures occurred frequently, especially following injection of cultures from recently infected dental pulps and apices of teeth in which there was little or no demonstrable rarefaction, but search for lesions in the teeth was not always made, and hence the percentage incidence is not included in the table.

The statistics in the table, striking as they are, do not adequately express the remarkable specificity of some of the strains, especially with regard to the kind of lesions produced. Thus, if the condition in the patient was relatively acute, the lesions in the animals were prone to be more pronounced. In the cases of neuritis the lesions were situated within the nerve substance, with little or no surrounding inflammation, and were especially numerous in peripheral nerves. This was particularly true in one case of a prolonged marked attack of peripheral neuritis.

The results in 6 cases of sciatica were quite different. Here localization occurred chiefly in the sheath of the sciatic or other large nerve-trunks and surrounding the posterior roots. These lesions were associated usually with marked edema, hemorrhage, and infiltration, extending into the surrounding structures.

The elective affinity of the streptococci from foci in myositis was so marked that the organisms not only tended to localize and produce lesions in muscles, but the location of the lesions often approximated that noted in the patient. When the affection of other structures, such as joints and nerves, appeared as a secondary factor in the symptomatology, lesions were also found in these structures in the injected animals, and the percentage of

animals with them was proportionately less than the percentage of animals with muscle lesions.

In pregnant rabbits localization was found to occur not only in the muscles of the parent rabbit but also in the fetuses.

Localization in the myocardium, especially in the bundle of His, with the development of arhythmia of the heart following the injection of cultures from pyorrheal pockets in a case of impaired myocardial conduction not due to syphilis, is another striking example of the extreme specificity of some strains of streptococci for certain tissues.

This narrow specificity for certain tissues is in keeping with the fact that myositis occurs during certain epidemics of respiratory infections, and with the striking example of elective localization in a wide-spread epidemic of myositis reported by Curschmann, in which the muscles of the neck were chiefly involved.

The foci studied included pyorrhea, apical infections around the teeth, suppurating dental sinuses, pulpless teeth without rarefaction at the apical end, suppurating sinuses of the head, infected tonsils, and infections of the prostate gland. Not all foci yielded streptococci having elective localizing power. In some cases both dental and tonsillar foci harbored them; in others one or more foci in the dental area only; while in others the tonsillar foci yielded streptococci giving positive results when the dental foci did not. Evidence has been obtained which indicates why infections in certain foci, such as those at the apical end of devitalized teeth, remain symptomless and at the same time may be the source of metastatic infections. Microscopic sections show that the bacteria are not usually encapsulated in the thick wall of connective tissue of granulomas remote from blood-vessels, as is commonly assumed. They are situated chiefly along the periphery and near newly forming blood-vessels. Opportunity for drainage into the circulation appears ample, swelling and tension do not occur, and hence the focus usually remains unsuspected because there are no local symptoms.

At this point I wish to call attention to some observations which I believe have an important bearing on the entire problem of focal infection and which support the idea that foci of infec-

tion not only incite a forced relationship between bacteria and the resisting mechanism of the host, but furnish the conditions favorable for them to acquire high and peculiar infecting power. It has happened repeatedly that streptococci in cultures from the pus in well-formed abscesses in extirpated tonsils, and from the pus exuding from pyorrhea pockets failed to produce lesions when at the same time the streptococci in cultures from emulsions of the washed tonsils and from the pus aspirated from the depths of the pyorrhea pockets localized and produced lesions in the tissues corresponding to those involved in the patient. Cultures on blood-agar and smears failed to reveal any noteworthy difference in the two sets of cultures. Similar results have been obtained when cultures from foci in teeth and tonsils and from the surface of the throat or buccal mucous membrane were injected simultaneously. In the former, positive results were obtained; in the latter, slight or no localization occurred. Prolonged contact of bacteria with leukocytes in pus, and a high oxygen pressure in mucus on the surface of mucous membranes, appear to reduce the invasive powers of the bacteria.

Certain interesting and suggestive results have been obtained in goiter, vagotonic neurosis, lesions of the pancreas, lesions of the eye, endocervicitis, and nephritis, which indicate that focal infection and elective localization may have a part in the production of these diseases, which are not usually thought to be of infectious origin.

GOITER

A series of animals has been injected with fresh cultures of the diphtheroid-like streptococcus which I have isolated consistently from the thyroid gland and excised cervical lymph-gland in cases of goiter. Of the 68 animals injected with strains from 16 patients (10 who had exophthalmic goiter and 6 nontoxic goiter), and examined soon after injection, 34 (50 per cent.) had gross lesions in the thyroid. The incidence of lesions in other organs was about the same as that observed in other similar experiments. Microscopically, marked dilatation of blood-vessels and hemorrhage in the interstitial tissues or acini were found in 10 of 14 dogs, 11 of 13 rabbits, and 5 of 8

guinea-pigs injected in from one day to four days previous to necropsy. Bacteria were usually not demonstrable. In a series of 16 dogs that were injected repeatedly and allowed to live for from twenty days to seventy days after the first injection, loss in weight and enlargement of the thyroid gland occurred, and diarrhea developed. One developed, in addition, softening, pulsation, and bruit of one lobe of the thyroid, associated with marked tachycardia and tremor.

A watery appearance on cross-section of the thyroids was usual in the animals that developed symptoms. Microscopically, there were found vacuolization and irregular staining of the colloid, colloid within vessels, areas of necrosis, and a variable degree of hyperplasia, which in some instances was extremely marked. Micro-organisms were either few or not demonstrable.

VAGOTONIC NEUROSIS

Three patients suffering from vagotonic neurosis have been studied from the standpoint of focal infection and elective localization. In each of these cases one or more animals injected intravenously with cultures from the pus expressed from the tonsils developed hemorrhage and edema due to localization of streptococci in the vagus or sympathetic ganglia or nerves. In one of the animals hemorrhage and edema were found in the splanchnic nerves, associated with hemorrhage and ulceration of the mucous membrane of the stomach.

LESIONS OF THE PANCREAS

Acute pancreatitis occurs commonly in epidemic parotitis, and less often in epidemic influenza. Interstitial pancreatitis, associated often with cholecystitis, is thought to be the result of ascending infection through the pancreatic ducts, since the lesions are usually more marked in the head of the pancreas. During the course of my experiments on the effect of intravenous injection of streptococci from a wide range of sources certain interesting results have been obtained which may have a direct bearing on the pathogenesis of diseases of the pancreas.

Lesions of the pancreas occurred in 26 per cent. of 19 animals

injected intravenously with the streptococcus isolated from Steno's ducts in epidemic parotitis, in 3 per cent. of 168 animals injected with the ulcer strains as isolated, and in 17 per cent. of 39 animals injected with these strains after several animal passages, in 5 per cent. of 41 animals injected with the cholecystitis strains as isolated, and in 19 per cent. of 16 animals after animal passage. In rheumatic fever the incidence was 3 per cent. of 71 animals following injection of the strains as isolated, and 21 per cent. of 19 animals injected after animal passage. Only 3 of 217 animals had lesions of the pancreas following injection of streptococci as isolated and after animal passage from appendicitis, herpes zoster, erythema nodosum, and myositis. In some instances reinjection into a series of animals of the streptococcus isolated from the experimental lesions in the pancreas was followed by localization in this organ. Thus, in one instance the green-producing streptococcus from influenza produced hemorrhagic pancreatitis after one animal passage. The strain from the pancreas was then injected intravenously into 2 guinea-pigs and 2 dogs. One guinea-pig and one dog developed hemorrhagic pancreatitis. When lesions of the pancreas developed they were usually severe and most marked in the head, and consisted of edema and diffuse and circumscribed hemorrhages, usually associated with fat necrosis. Sections of the pancreas showed separation and degeneration of parenchymatous cells, edema, hemorrhages, infiltration of interstitial tissues, partial or complete plugging of capillaries, with swollen and desquamated endothelial cells, and diplococci. There was relatively little change in the parenchymatous cells or the islands of Langerhans.

In several patients with cholecystitis and pancreatitis in whom there was a low glucose tolerance pancreatitis followed injection of streptococci from dental and tonsillar foci. The experiments support the idea that interstitial pancreatitis may be due to streptococci that gain entrance through foci of infection harboring bacteria which have elective affinity for this organ, and that ascending infection does not always occur. The possibility that the degeneration of the islands of Langerhans in pancreatic diabetes is due to organisms having elective affinity for

these structures is suggested by these experiments. The history of acute infections, sometimes referable to the gastro-intestinal tract, some time previous to the onset of diabetes, especially in children, also suggests this possibility. The idea has been put to the test on repeated occasions during the past six years.

Localization of a colon bacillus isolated repeatedly from the ethmoid sinus of a patient with diabetes who was always worse following exacerbation of the sinusitis, occurred in the pancreas in each of 5 rabbits injected, and in 4 of 6 rabbits injected with a streptococcus from the tonsils following tonsillitis of a patient with acute diabetes. In these the lesions were similar to those just described and no predilection for the parenchyma and islets was demonstrable. In another patient with acute diabetes, with a history of tonsillitis, localization of a streptococcus from the extirpated tonsils occurred in the pancreas in rabbits in the second animal passage, but not in the third. In this instance the gross lesions in the pancreas were relatively slight. Microscopically marked evidence of damage, swelling, granular degeneration, irregular staining, and vacuolization of parenchymatous cells were found, but there was little interstitial infiltration. In 3 cases in which there was no clinical evidence of focal infection cultures from tonsils and teeth gave negative results.

LESIONS OF THE EYE

In a previous paper[31] it was shown that lesions of the eye, such as iritis, usually occur only when streptococci have attained a certain degree of virulence. Since then iritis has been produced in rabbits with streptococci isolated from the infected pulps of teeth in patients suffering from iritis. The possibility that recurrent intra-ocular hemorrhages, often resulting in complete blindness, might be the result of focal infection was put to the test in 2 patients. In one the culture for injection was obtained from the vital pulp of a badly decayed tooth; in the other, from a suppurating sinus surrounding the left lower third molar. Of the 9 rabbits injected, 6 developed lesions of the eye. In one panophthalmitis, with hemorrhage in the retina, resulted. In the others swollen whitish areas and hemorrhages in the retina

were demonstrated with the ophthalmoscope or by microscopic examination of sections. Streptococci were demonstrated in the lesions. Ophthalmoscopic examination of a series of rabbits injected with cultures from foci in other diseases revealed no lesions of the eye. It should be noted that in one of these patients the vision followed in a remarkable manner the stoppage or drainage of the pus exuding from the tooth. With lack of drainage even for a day the vision diminished on repeated occasions, and increased when drainage was again established.

ENDOCERVICITIS

The idea that endocervicitis might be the result of a hematogenous infection took definite form through a striking result in the case of a little girl, three years of age, who developed a purulent vaginal discharge during an attack of influenza in the 1918 epidemic. Smears and cultures of the vaginal pus yielded large numbers of the green-producing streptococcus so commonly found in that epidemic. Intratracheal injection of the primary and secondary cultures, besides producing hemorrhagic edema of the lungs, produced lesions with purulent exudate proved to be due to the streptococcus in the uterus and vagina in each of 3 female guinea-pigs injected.

With the assistance of Dr. Moench a series of cases of endocervicitis have been studied from the standpoint of elective localization.

A partial tension streptococcus was found in large numbers in cervical or vaginal pus in each of the 9 patients, chiefly young women, thus far studied. Intravenous injection of this organism into a series of animals was followed by localization in the cervix, uterus, or vagina, often with the formation of large amounts of pus, in all but one of these cases. Only one rabbit was injected in the negative case. In 4 cases localization occurred in the cervix, uterus, or vagina of animals following injection of streptococci from infected teeth; 3 of the patients were well otherwise, while 6 suffered besides from symptoms of arthritis, myositis, or sciatica. In these, as in myositis, localization occurred also in the joints, muscles, or nerves in some animals.

NEPHRITIS

There are many facts which indicate that nephritis may frequently be the result of focal infection. Lesions of the kidney were prone to occur first after non-virulent laboratory strains of streptococci had attained a certain grade of virulence from animal passage. An incidence of lesions, 20 per cent., chiefly in the cortex, followed injection of the *Streptococcus viridans* from endocarditis. The incidence of kidney lesions, while low, varied considerably following injection of streptococci in the different diseases studied (Table). It was highest, as shown previously,[29] following injection of the rheumatic fever strains, 39 per cent., and, as pointed out, the type of lesions was such that their repeated occurrence might ultimately result in a scarred, contracted kidney which develops not infrequently in patients with recurring attacks of rheumatic infections. The affinity for the kidneys became greater after the streptococci from appendicitis, ulcer, and cholecystitis were passed through a number of animals. Thus, it was 2 per cent. following the injection of 277 animals with these strains as isolated, and 10 per cent. of 77 animals injected after the strains had passed through several animals.

I wish now to report the results following intravenous injection of cultures from foci of infection in 4 cases of nephritis, representing different types of this disease. Altogether 33 animals (16 rabbits, 15 guinea-pigs, and 2 dogs) were injected with the cultures as isolated. Of these, 27 (82 per cent.) developed lesions of the kidneys. The affinity of these strains for the kidneys in the second animal passage was also marked, while in the case of two strains in the third animal passage it had largely disappeared. The lesions in other organs were few.

The kidneys of animals injected with the streptococci isolated from the prostatic fluid, shreds in the urine, and from the extirpated tonsils in a case of chronic interstitial nephritis showed only slight changes aside from small necrotic areas, chiefly in the cortex. Following injection of the streptococcus from the tonsils in 2 and the dental foci in 1 of 3 cases of acute nephritis the kidneys developed larger, more acute focal lesions in cortex and

medulla, and moderate diffuse edema and cloudy swelling. Streptococci were easily demonstrable in the focal lesions, but not elsewhere; and even in the necrotic areas they tended to disappear after forty-eight hours following a single injection.

In a number of experiments a selective survival of these strains in the kidneys was demonstrated by making differential cultures of various organs in animals sacrificed at intervals after injection. Thus, in a case of acute nephritis the green-producing streptococcus isolated from the tonsil produced nephritis in a rabbit and in a guinea-pig. The strain from the kidney of the rabbit was again injected intravenously into a rabbit and a guinea-pig. Forty-eight hours later when the animals were chloroformed numerous embolic lesions and diffuse edema were found in the kidneys; 3 additional rabbits were injected. One of these was sacrificed in ten minutes, one in twenty-four hours, and one six days after injection. The one killed in ten minutes had numerous exceedingly small hemorrhages in the lungs. Comparable cultures from emulsions of muscles, mucous membrane of stomach and brain contained no bacteria. The left ventricle yielded 15 colonies, the lungs, spleen, and kidneys about 10,000 colonies, the liver countless numbers, and 0.5 c.c. of the urine and blood each 35 colonies of streptococci. The one killed in twenty-four hours had localized areas of hyperemia and edema in the kidneys. The culture from the muscles, lungs, mucous membrane of the stomach, brain, and blood did not yield growth. The spleen contained 3 colonies, the liver 7 colonies, the kidneys countless numbers, and the urine 500 colonies of streptococci. The rabbit killed in six days had a large number of small embolic abscesses in the kidneys, situated beneath the capsules and surrounded by hyperemia, and a few lesions in the myocardium.

With the assistance of Dr. Meisser a case of advanced nephritis with marked renal dysfunction has been studied. In this case the conditions in the patient were closely simulated by establishing foci of infection in animals. The patient had repeated attacks of exacerbation of the nephritis following attacks of nasal and tonsillar infections for a number of years previous to our study. Cultures made at various times from the meatus

of the nose, from washings of the maxillary sinus, and from the tonsils yielded chiefly a staphylococcus which, on intravenous injection, had marked affinity for the kidneys of rabbits, producing marked focal nephritis in 30 of 32 injected. Tonsillectomy was advised on the basis of these results and marked improvement in the patient's condition followed removal of the tonsils. The strain from the tonsils retained its affinity for the kidneys through six animal passages. It was thought that this strain might possess the qualities necessary to produce nephritis if placed in devitalized teeth.

The two lower cuspids in 4 dogs were devitalized in a sterile manner under ether anesthesia. The pulp chambers were immediately infected with the primary culture from the kidney of one rabbit with marked nephritis following intravenous injection, and the opening in the tooth sealed with cement. The animals were well nourished and active at the time. The urine in all was normal They were fed a balanced diet of dog biscuit. There was no swelling and no apparent discomfort in the jaw following the devitalization. The teeth remained firm, the enamel became discolored, and areas of rarefaction over the apices, demonstrable by the *x*-ray, developed in each.

Catheterized specimens of urine were examined at intervals. One kidney was removed from each dog in from three to five weeks after devitalization of the teeth.

One dog died in two months and two days, and one in two and a half months following devitalization of the teeth. The other two dogs were chloroformed in two months and ten days, and in four months, respectively, after the teeth were devitalized. Rarefied areas at the apices of the devitalized teeth were found to be filled with edematous, moist scar tissue resembling granulomas, such as are found at the apices of devitalized teeth in man. The staphylococcus was isolated from these areas in each case. Focal but widely disseminated nephritis, involving both cortex and medulla, developed in each of the 4 dogs, and albumin, pus, and blood-cells were found in the urine. In 3 the lesions remained limited to the kidney, while in 1 marked pyelitis and cystitis also developed. The mucous membrane of the pelvis

and the bladder wall in this animal was edematous, infiltrated, and contained many areas of hemorrhage. Adherent to the mucous membrane were many long, non-laminated, rough, pumice-like concretions, extending in a fan-like manner from the base of the bladder up along the blood-vessels. The ureters contained a number of similar concretions.

The staphylococcus, which again produced lesions of the kidney in rabbits on intravenous injection, was isolated from the kidneys in all.

The result in the dog that developed marked calcareous deposit over the inflamed areas in the bladder suggests strongly that infection by bacteria having elective affinity for the urinary tract may be an important factor in the formation of stone. Of interest in this connection is the fact that a sheep injected daily intravenously for several months with doses of dead streptococci from pyelonephritis had numerous concretions in the pelvis of the kidneys. Some of these were free; others were still adherent and embedded in the localized exudate in the pelvic mucous membrane.

CONCLUSIONS

The results of my previous work on focal infection and elective localization have been corroborated and extended. The experimental investigations emphasize again the importance of this mechanism of infection and the need for painstaking effort to find and remove, when possible, foci of infection in the treatment of many diseases.

The fact that streptococci having elective affinity have been isolated repeatedly from pulpless teeth that did not show rarefaction at the apices indicates that these supposedly harmless areas should be considered as possible sources of systemic infection.

Just as certain types of streptococci tend to remain limited to particular areas in the throat, such as the hemolytic streptococcus to the tonsils, so strains having specific localizing power tend to remain limited to the focus. The experiments indicate that while the different strains of streptococci in a given disease have specific infecting power and other properties, they may

become sufficiently modified under the influence of changed environment to be the cause of different diseases.

The reasons for the presence in the foci of bacteria having specific localizing power, possibly in part due to peculiar environment afforded by the tissues, are still obscure, but that the specific localizing power is an important factor in determining the place of localization has again been demonstrated. The experimental production of a common type of chronic focus, the granuloma, and the production in consequence of one systemic disease, nephritis, with an organism having elective affinity for the kidneys removes the last objection to the acceptance of the theory of focal infection and elective localization.

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